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FORTHCOMING

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SOME TENETS OF MEDICAL EDUCATION[1]

LEWIS H. WEED

The Johns Hopkins University

It is indeed a very great honor which your Faculty has done me in asking me to speak at these Commencement Exercises of the Cornell University Medical College—an honor which intrigues me the more as I have been unable to decide whether it comes to me as a Dean of a Medical Faculty or as an Anatomist. The Anatomist, as you know, makes use of every opportunity to lecture before his classes in Gross Anatomy, in Histology, and in Neuro-anatomy; he prizes highly the chance of talking without restraining bonds to the earnest and eager medical student. The Dean, likewise, effectively develops every situation into one for informal and formal addresses—rarely contenting himself with the few introductory remarks to the entering class in medical school, and with the presentation of candidates for the degree of doctor of medicine. With this common urge for public utterance, it would seem that there is no essential conflict between the desire of the Dean and of the Anatomist to address a graduating class, although the one is thought to be interested in the theory and practice of medical education, and the other in teaching a basic science to medical students. But as the medical Dean, with his ecclesiastic ancestry, always maintains his fundamental office in the ceremonies of graduation, it seems to me entirely appropriate that I should talk of some of the tenets of medical education as viewed by an Anatomist, who unlike his administrative superior is unhampered by historical limitations. Perhaps indeed the viewpoint which I shall give is an admixture of these conflicting impulses and educational tendencies, harmonized as far as possible within the mental processes of a single individual.

It is not my purpose to speak on this occasion of the opportunities before the members of a graduating class in medicine. These opportunities are manifold: they extend today throughout the wide range

[1]Address given at the Commencement Exercises of the Cornell University Medical College, New York City, June 13, 1929.

of public health service; of medical practice; of the medical specialties; of teaching careers, both in the clinical and preclinical subjects; of military and naval medicine; of hospital administration; of pure medical research; and of a multitude of other very special medical vocations. In all of these fields there are promising openings for the energetic and well-trained medical graduate; in all there are splendid chances for the individual to show intellectual capacity and technical skill. Success in any of these undertakings is, of course, dependent upon opportunity and upon ability, but this success may be accelerated or retarded by the nature of the training which the medical graduate has enjoyed. And so the quality of instruction in a medical school may be somewhat accurately judged by the provision made for the proper grounding of its students in modern medicine. Not only is it incumbent upon medical schools properly to teach the art of the practice of medicine, but also it is equally important to encourage in students an enthusiastic, discriminating attitude towards the problems of medicine.

With realization of this important function of the medical school, it seems easy to comprehend the desires of the Anatomist to maintain the initial position of the teaching of Anatomy in the medical curriculum. It may be asked, quite properly, why the Anatomist so relishes this place in the four years' course; and it would appear that the answer is not difficult. As far as the graded curriculum is concerned, it is of course essential that knowledge of anatomy should precede instruction in physiology and pathology, but it is hardly necessary that much anatomy should be given to medical students before they enter upon their courses in bacteriology and physiological chemistry. Essential, as it is, that anatomy should be the first subject of medical instruction because on morphology depends so much of subsequent medical teaching, there is still another reason for the Anatomist to cherish this position in the medical curriculum.

This basic reason largely has to do with the opportunities before the medical teacher when the students are introduced into professional education, for the Anatomist really has never felt himself limited to his field of medical instruction—greater dreams have always been before him. He wishes to cultivate a method of thinking, and while he glibly uses the term "teach," he really feels that he can teach but little:

all he can do, in the final analysis, is to offer the best possible opportunity for the student to learn. In the dissecting room and in the histological laboratory, the Anatomist tries to present his particular subject as a problem in science. The student is provided with the material, whether it be the human cadaver, whether it be the microscopic section or the fresh preparation to be studied histologically; and by precept, the student is given a method of analysis, with scalpel and forceps or with microscope and teasing-needle. The teacher acts merely as a type of directional agent, steering the student away from the hazards of careless work which result in the ruin of material, and leading him into the more profitable ways of scientific analysis.

Primarily, the Anatomist seeks to arouse in the student what we like to term "the spirit of inquiry"—the spirit of scientific curiosity. The success of the teacher is largely dependent upon his ability to incite and foster this spirit of inquiry, for unless the student soon acquires this questioning habit of mind, he will go through the courses of instruction in a somewhat blind way, learning ultimately tricks of medical diagnosis and therapy, but without essential understanding of the true function of a student of medicine. So the Anatomist, because of the early need of morphological knowledge and because of the peculiar materials of his subject, feels that he has an unique opportunity to allow the student to learn something of a particular science, to direct his efforts, and to lead him to develop his own scientific curiosity.

Such a spirit of inquiry is needed not only in the course in anatomy and in the other preclinical sciences, but it constitutes an essential element of the most desirable attitude towards the art of the practice of medicine. For the graduate in medicine, out from his own professional school, must carry with him an inordinate, unrestrained, interrogative interest in the many problems which challenge him every day, whether these be in medical teaching, in public health work, in medical practice, or in pure research: the same spirit of scientific curiosity must be the directing impulse.

If the assumption is accepted that the excitation of the spirit of inquiry should be deemed an essential element of medical instruction, one may wonder why the courses in Anatomy afford the most desirable

opportunities for development of viewpoint in the student. I have emphasized already the usefulness of anatomical material towards this end; the student without great loss may grope around for some weeks in the dissecting room or histological laboratory, learning a method of study and acquiring a mental attitude without great damage to the material. Coming into a professional school after two or more years in college, the student suddenly encounters the tremendous bulk of information in the preclinical sciences. Even in the best of the American colleges, the student has been carefully protected and instructed; rarely has he gotten away from the almost paternalistic attitude of the instructional staff. With definite assignments from day to day, the college student has had the satisfaction of supposedly completing his preparation from month to month; and then abruptly in the medical school he finds that his work is no longer completed at the end of each day. He finds himself in professional work.

The Anatomist, piloting this college student at the inception of his medical course, feels that Anatomy must of course be presented in a truly professional way. Although the professional school has limitations with which the graduate school of a university is not primarily afflicted, the best instruction in the medical curriculum is today of the same type as in the graduate departments of the natural sciences, or of the humanities. In all of these university subjects of learning, the student is given the opportunity to acquire some of the basic data of the problems of one of these fields. He studies the hypotheses, the speculations, the tenets, the deductions which have been drawn from the data already gathered, but he is not forced to accept any of the conclusions. He is taught the limitations of deductive and inductive methods, but he is allowed to make up his own mind regarding the many unsolved questions of that branch of knowledge.

If a medical faculty desires to conduct the courses of instruction in its school along the lines of graduate study, it must first realize that the professional school is usually restricted by having certain legal requirements confronting its candidates. In this respect the professional school differs from the graduate school in philosophy or science. Schools of medicine, as those of law, have only a moral obligation towards the community and no legal restrictions; the moral obligation is, however, considered by medical faculties to be binding.

The legal means of protecting the public against ill-trained practitioners of medicine has been taken, and quite properly, from the medical schools and lodged in State Examining Boards. The attitude of these State Examining Boards has been very generous and liberal: they have not in any way attempted to interfere with the arrangement of the medical curriculum or with the habit of mind developed in the medical student. These Boards hold that their function is to pass upon the quality of the final product rather than upon the means towards the end. And while at times there have been tendencies towards standardization of curricula and towards standardization of courses and contents of courses, medical schools have not suffered from any restrictive legislation. The schools are free, then, to try to do their particular jobs of medical instruction in the way in which their facilities, their faculties and their finances permit. In other words, medical schools are free to develop as different types of institutions,—a very beneficial circumstance for the ultimate progress of medicine in this country.

Thirty years ago, the body of scientific fact in medicine was small enough to permit adequate presentation to medical students within the course of four years, and in the old proprietary medical school the teaching largely centered upon the art of medicine, with lectures on many subjects pertaining to successful practice. When the reformation of American medical instruction, begun in the early nineties, reached its height in the first decade of this century, the curricula of medical schools were in no way overloaded. After allocating all of the hours requested by the anatomist, by the physiologist, by the pharmacologist, by the pathologist, and by the teachers in the clinical subjects, there still remained unassigned many hours in the four year course.

At this time the practice of medicine was based largely on a single science—pathology—but something over two decades ago, medical practice began to take cognizance of the basic relation of chemistry and physics to its problems. New procedures of diagnosis, developed largely upon exact methods from these two sciences, became imperative for the proper study and care of patients. Almost simultaneously, various special interests in the medical and surgical departments began to assume individuality as specialties, each with its own peculiar body of fact and each with its own special diagnostic methods and dis-

tinctive therapeutic procedures. The whole problem of medical practice changed within a few years and the patient came to be looked upon not only as an ill individual requiring the attention of physicians, surgeons and usually of specialists, but also as an individual whose mental well-being had to be considered and whose economic problems needed the attention of skilled social workers. These tendencies and new requirements for medical practice found expression in the establishment of bacteriological, physiological and chemical laboratories within the medical clinics, and in the development of special subdivisions within the surgical departments, as well as in the close integration of psychiatric institutes with the general clinical services and in the wide-spread creation of social service agencies throughout hospitals. The increasing realization of the mental factors in disease was quickly reflected in the teaching of psychiatry throughout the medical curriculum, and basic courses in psychobiology were found to be essential for the proper introduction to clinical study in this field. More recently, these tendencies, which have grown strong roots in some university medical schools during the past twenty years, have been gathered together into so-called institutes of human behavior or human relations, where the physical, mental and social aspects of human beings are to be studied intensively. Such tendencies can only with difficulty be reduced to cooperative organization: they arise by spontaneous realization of the mutual opportunities for service which exist within the various departments, interested in the many phases of the whole complex problem.

And so, with all of these great trends now before the student as he enters upon the four years of medical instruction, it is not strange that he should find himself almost overwhelmed by the mass of scientific data of which he can at best hope to acquire but a small portion. In other fields of education, a healthy reaction has taken place, and it has recently been given admirable exposition in a short article by Professor A. N. Whitehead on the "Aims of Education." Here, Whitehead tells us that the first commandment to be obeyed in any educational scheme is this: "Do not teach too many subjects," and the second commandment is this: "What you teach, teach thoroughly." Whitehead argues strongly for these two dicta, showing that, after all, learning is something more than a mere smattering of facts, something more than

scraps of information. In the words of an old Latin saying: "The knowledge of smatterers is mixed ignorance." Whitehead would have us do away with the acquisition of "inert" ideas, considering that this process is not only useless but that it is actually harmful. The only information which he would have us give is that which is useful and active.

As teachers devoting ourselves to medical education—professional medical education rather than the purely technical—we must discover whether Whitehead's concepts pertain equally well to our own educational problems. Most medical instructors will agree that we have tried in the past to teach too many subjects, to force into the minds of our students scraps of information which may or may not stay, and which in some measure at least are useless, non-active, inert facts. If this generalization be accepted, then necessarily we must seek to remedy our faults in the administrative policies which underlie the assignment of hours for required instruction and the whole arrangement of our medical curricula.

The enlargement of the field of medical knowledge during the past three decades led naturally to equivalent increase in the complexities of the medical curriculum. With the accession of information in the various preclinical fields, more and more required hours were demanded by the instructional staffs in these subjects; and in the clinical departments exactly the same phenomenon occurred. In the basic subjects of general medicine and general surgery with the newer, more complicated methods of diagnosis and treatment, the hours allotted for teaching seemed increasingly inadequate. The specialists, even in minor and restricted fields of clinical practice, requested obligatory hours; and these hours were granted as the specialties assumed greater and greater importance in practice. These processes resulted in a gradual mounting of the total number of required hours of medical instruction, so that the student rushed from laboratory to clinic, to didactic lecture, from morning until night, during his nine months' annual course over the four year period. The body of scientific data and the information required for skillful practice were overpowering; and in medicine, as in other branches of human knowledge, the pendulum swung much too far towards the overburdening of the student with required instruction.

All during this period, medical teachers were talking and writing of the necessity for liberty in medical education, but few faculties were really conceding it. Reaction to the over-crowding of the medical curriculum came largely with acceptance of those basic ideas in professional education which I have already developed. First of these is the creation of the questioning habit of mind, the spirit of scientific curiosity; then, secondly, the realization of the function of a teacher as a piloting agent who offers the opportunity for the student to learn; and lastly, avoidance of too much teaching in too many subjects, but with this teaching at the highest possible level. Development of a medical school with these underlying ideas requires, most of all, an excellent faculty of an investigative bent, and then good laboratories, abundance of material, good clinics with many patients. With such a faculty and with such facilities, the course of required instruction may be so arranged that the student has freedom of time for thoughtful analysis and synthesis of the body of fact which comes before him—liberty for pursuit of this own personal inquiries.

As an Anatomist, these general conceptions of professional education in medicine do not alarm me. As a Dean, I realize that a curriculum arranged upon these lines means, not a slight reduction of required hours from the level of ten years ago, but a drastic cut with rearrangement of the whole plan of instruction. Such a conflict of emotions is, however, not fundamentally serious to either the Anatomist or to the Dean who believes in the experimental method, for surely experiments with educational procedures on a group of students are as necessary as experiments with physiological procedures on other material.

So with such controls as could be had, the experiment was set up in the school with which I am connected; a new curriculum, expressing these conceptions of professional education was devised. With approximately 5100 teaching hours available in the four years, it was found desirable to reduce the number of required hours to a minimum, in order to give the student sufficient free time; and this minimum was fairly accurately gauged as constituting one-half of the total time in the four year curriculum, so that the obligatory courses aggregated slightly over 2500 hours. The exact distribution of this required instruction was of course dependent upon local opportunities and local reasons, as well as upon the general conceptions.

To reduce the required work in the four year curriculum to this level, it is necessary that the departmental teaching be limited to basic courses in which the essential elements of the subject are alone presented. Superimposed upon this basic instruction should be ample opportunities for additional courses in the required subjects, for elective courses in all branches, and for other work of the student's own choosing. As the scheme would work out on a skeletal curriculum of such minimal required courses in the fundamental departments of medical instruction, the minor medical specialties (and I use this term in contradiction to the major medical specialties, as generally determined) would have no required hours except as assigned to them in the major courses of clinical instruction. But every student would have the diagnostic procedures, characteristic of the specialties, presented to him in a course given at the same time as the elementary instruction in physical diagnosis. The students would be enabled to gain additional knowledge of these subjects by electing to spend the free time in courses devoted to the special fields. The distribution of free time in such a curriculum would largely be concentrated into various periods, in order that it may be more effectively employed. Thus, in the first year of medical instruction the free time would hardly be of great service, but by the end of the second year of instruction and in the subsequent years, a great deal of free time could be used to marked advantage.

Such a curriculum, while presenting in some ways nothing of novelty except marked reduction of hours, should permit the development of individual interests to an extreme degree. The student would be privileged to select what may be termed a "departmental program," whereby, in conjunction with the head of the department or with the administrative officer of the school, he would plan a course, using the required and free hours and leading to a splendid training in the particular subject to which he wishes to devote his life. Experience has shown that with the proper development of initiative, the student dislikes consultation with the administrative or scholastic officers, and he plans his own course frequently to the best advantage. Some students, however, choose to devote themselves to a heterogeneous preparation, either because of the fact that they have not as yet determined upon their particular field of activity or because they are

resolved upon a career in general practice. For either of these purposes, such a free curriculum allows the varied training, with a smattering of many specialties, that seems essential for the student as he goes into general practice. Analysis of the use of free time has revealed that roughly one-fourth of a typical class will take such diversified courses and will not concentrate on either the type of instruction offered by the departmental program, or the training in the fundamental sciences which certain research careers demand.

Student comment regarding this curriculum may be divided into three main lines of thought: One group of students, representing in general the best type, is thoroughly happy at the great amount of free time afforded for special work of one's own choice. It is this type of student who becomes essentially interested in some one subject during his student days and who later develops into an outstanding clinician or into the university type of medical teacher. The second group of students feels that the curriculum operates quite well but would like to have more opportunity for additional elective work in all subjects, particularly in the way of practical work in the clinical branches. This group comprises the larger part of the class and is composed of the good students, on whom in the final analysis the reputation of the School must rest. The third group of students is not so large; it is in general composed of the poorer members of the student-body. This group wishes to have every minute of the day taken up with practical courses; it is the group which ordinarily thrives on thoroughly didactic teaching.

Of almost equal importance to the relative freedom of choice is the opportunity which such a curriculum affords for the migration of students to other institutions. With the proper arrangement of the required courses and with the student taking full advantage of the selections, it is possible to leave the school of registration for periods up to nine months (including in this interval a summer vacation). Such privileges enable energetic matriculates to go to Europe for work in any of the major subjects of instruction, to devote themselves to courses at other American institutions, or to train themselves in special work under investigators of their own choosing. The difficulties encountered in inducing American medical students to migrate for a while are really remarkable; and it is equally remarkable what advan-

tages accrue to them by study under masters other than the ones in their own schools. Such migration of students has of course been known in the mid-European universities for over a generation: there is nothing in German medical education which contributes so effectively to diverse viewpoints and broad training as does this migration from institution to institution and from professor to professor.

Although it seems to those of us actively engaged in medical education an admirable thing to have a liberal curriculum, it is realized that such a curriculum is merely a means towards an end. Machinery of administration is necessary in order that the students may in proper numbers be conducted through a graded four years' course without undue loss of time, but the machinery is, after all, entirely artificial and secondary. Too much administrative procedure leads to too much of the rigid progression, class by class, through the medical schools—the all-too-common phenomenon of the lock-step as Flexner termed it. The real problem of medical education lies not in the curriculum but in the quality and attitude of the instructional staff. As long as the medical instructor feels his responsibilities as a piloting agent and avoids the supreme error of dogmatism, medical courses may be given in an effective manner—more effective as more of the instruction is in the nature of example and precept to small groups. Here the opportunity to learn may be offered to the student in splendid fashion. The instructor becomes merely a senior student, who has retained in his own investigations his spirit of inquiry—his spirit of scientific curiosity—and he undertakes with the student in his small group the same methods which he employs in solving his own research problem, whatever its nature. The well known guide, philosopher and friend may be the rôle for the medical instructor, but even more important than this relationship is the atmosphere created by the questioning spirit of the true teacher-investigator.

Under these conditions it seems inevitable that some medical students should embark upon their own little problem—whether in the required work or in a simple investigation. On such an undertaking the student may acquire a first-hand knowledge of a little corner of medical fact and theory. The important thing is not the contribution which the student may or may not make; the important thing is the method of thought which he is forced to use in his attack on the prob-

lem. Such research-effort will lead the qualified student into a real comprehension of the procedures by which new knowledge is gained, into appreciation of the control of clinical observation or of experimentation, into the bibliography of his subject, and finally into some quite definite conclusions of his own. The advantages of the undertaking are apparent, yet only relatively few medical students should feel it incumbent upon them to embark upon a research problem. The urge to investigate is after all merely a slight accentuation of the spirit of scientific curiosity, which should run through the mind of every medical student. Viewed from this angle it is inevitable that with a stimulating atmosphere towards scientific advance, with proper facilities available, a certain number of students should respond to the urge to research.

So we have come back to some of the viewpoints of the eighteen nineties, when for the first time in America the medical student was carried away from didactic teaching of an art and was given an opportunity to learn by practical work in laboratory or in clinic. Our conduct of medical education since then has been somewhat tortuous and we have at times abandoned many of the guiding tenets of professional education. The medical matriculate still manages to graduate, even though his curriculum has followed all too closely the increasing complexities of modern medical practice and the increasing fund of knowledge in the medical sciences. Yet with all the limitations of professional education and with rapidly growing bodies of scientific fact, the medical teacher must avoid the narrow training of students solely as skillful, technical machines, thoroughly competent to practice medicine. Such medical graduates would leave their schools lacking the most desirable attitude of mind towards medical problems and without an equally desirable interest in the humanistic side of medicine. Rather should medical schools strive today to create and foster the inquiring student of medicine, who will carry with him his scientific curiosity throughout his life. The medical graduate may then become, through habit of thought and through influence of his medical training in such a school as this, a life-long student, enjoying the work of his profession and contributing much to medical progress.

STUDIES IN THE REACTIONS OF SIMPLE GOITRE TO IODINE

BRUCE WEBSTER, M.D.

From the Department of Medicine of the Johns Hopkins Medical School

In a previous communication (1) the effect of the administration of relatively large quantities of iodine to rabbits with hyperplastic thyroid glands has been reported. It was found that the exhibition of iodine to these goitrous animals caused a marked increase in metabolic rate. This was accompanied by rapid emaciation and very often terminated in death. The severity of the reaction bore a direct relationship to the extent of hyperplasia which existed in the gland before the administration of iodine was begun. The iodine tended to bring about involution of the hyperplastic glands and the extent to which this occurred seemed to depend directly on the time which elapsed between exhibition of the iodine and the death of the animal. It appeared that, in the metabolic and histological changes which occurred when iodine was administered to these animals, we had a means of studying the quantitative relationship between available inorganic iodine and the thyroid hormone into which it is transformed. The present communication deals with a study of the effect of the administration of iodine in single doses, in physiologically utilizable quantities, on the metabolism of animals with hyperplastic thyroid glands, and the histological changes which accompanied it.

Various aspects of the action of iodine on the hyperplastic thyroid gland have already been studied by several investigators. Marine and Feiss (2) in 1915 pointed out that the hyperplastic thyroid gland readily acquires iodine no matter in what form or manner it has been administered. In 1916 Marine and Rogoff (3) showed that the degree of hyperplasia of the gland was the chief factor which determined the amount of iodine taken up. Further experiments by the same authors (3) (4) demonstrated that the more hyperplastic glands would absorb approximately 1 mgm. of iodine per gram of thyroid gland, irrespective of any excess which might be available. They showed

that this iodine is stored in the thyroid gland almost immediately after it enters the circulation and that its incorporation into the thyroid hormone is much slower, requiring a matter of several days before it is completed. They further demonstrated that physiological activity of the iodine only begins when it is in organic form as hormone.

EXPERIMENTAL

The chief object of the present investigation was to study the changes in metabolism brought about by single, minute quantities of iodine injected into animals with hyperplastic thyroid glands, and thus obtain some idea of the relationship between available inorganic iodine and the hormone into which it is elaborated. A number of rabbits were chosen with thyroid glands of approximately the same size. These animals had all been in the laboratory for the same period of time and had all been subjected to the same standard conditions. Histological studies of the thyroid gland were made in the case of each rabbit, prior to the administration of iodine. Under ether anesthesia the gland was exposed and a piece of tissue removed. In each instance the amount of tissue removed was so small that the question of compensatory hypertrophy could be neglected. The estimated weight of the thyroid gland of all animals used in the first series was from 8 to 12 grams.[1] Microscopic sections of the tissue removed at this preliminary biopsy were almost identical in each case and will be described in detail later. The above precautions were taken in order to ensure, as far as possible, uniformity in the glands used.

The metabolic rate of these animals was then studied until a normal level was established. These determinations were made with a simple modification of Haldane's open circuit apparatus. The technique established in our previous studies (5) was followed here. When the animal's normal level of metabolism had been determined, a single dose of potassium iodide was then injected intraperitoneally and the changes in heat production studied. With Marine and Rogoff's demonstration that hyperplastic thyroid glands were capable of absorb-

[1] The estimation of the weight of the thyroid glands of rabbits during the biopsies was based on observation and measurements which were correlated with similar information obtained during several hundred autopsies, at which times the glands were afterward accurately weighed.

ing approximately 1 mgm. of iodine per gram of gland mass as a basis, we selected amounts of iodine which were well below this figure in order to ensure, as far as possible, complete utilization of the iodine given. Since the estimated weight of the glands used in the first series was from 8 to 12 grams, it is apparent that amounts of potassium iodide ranging from 1.25 to 5.0 mgm. should be well within those limits that have been proven physiologically to be utilizable. Accordingly, 1.25, 2.5, and 5.0 mgm. of potassium iodide were injected into respective series of animals and the metabolism studied until it remained at a constant level. A second biopsy was then performed on the thyroid gland, following which the same quantity of potassium iodide was again injected and the heat production again studied. This procedure was repeated until the injection of iodine failed to bring about any change in the animal's heat production. The effect of each of the three stated quantities of potassium iodide was studied in three separate animals with thyroid glands of approximately the same size. Later a second series was investigated in which the gland weight was estimated as being between 15 and 18 grams. During the entire course of the experiments the animals were kept under the standard laboratory conditions and upon the diet previously described (6). Care was taken to avoid all contact with iodine compounds, other than the amounts injected. Iodine was not used in the preparation of the skin for operative procedures.

RESULTS—METABOLIC

Owing to the length of the protocols which resulted from the above experiments, it is impractical to include them in full. Representative protocols from each series are included. The changes in heat production, which followed the administration of each of the quantities of potassium iodide, were similar for all the animals in each particular series.

Chart I shows the effect of 1.25 mgm. of potassium iodide on the heat production of three separate animals. It can be seen that there was an appreciable rise in heat production between the second and the fourth day after the first injection of iodine. The highest levels of metabolism occurred between the ninth and eleventh days after the injection. The chart further demonstrates that these maximum rises,

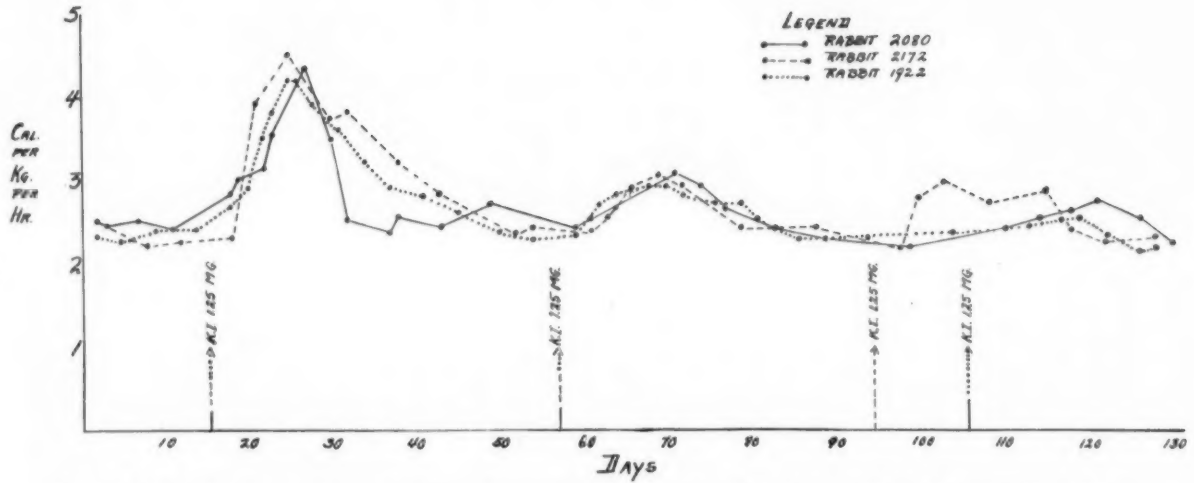


CHART I. THE EFFECT OF THREE SEPARATE INJECTIONS OF 1.25 MGM. of KI ON THE HEAT PRODUCTION OF THREE RABBITS WITH THYROID GLANDS OF APPROXIMATELY THE SAME SIZE

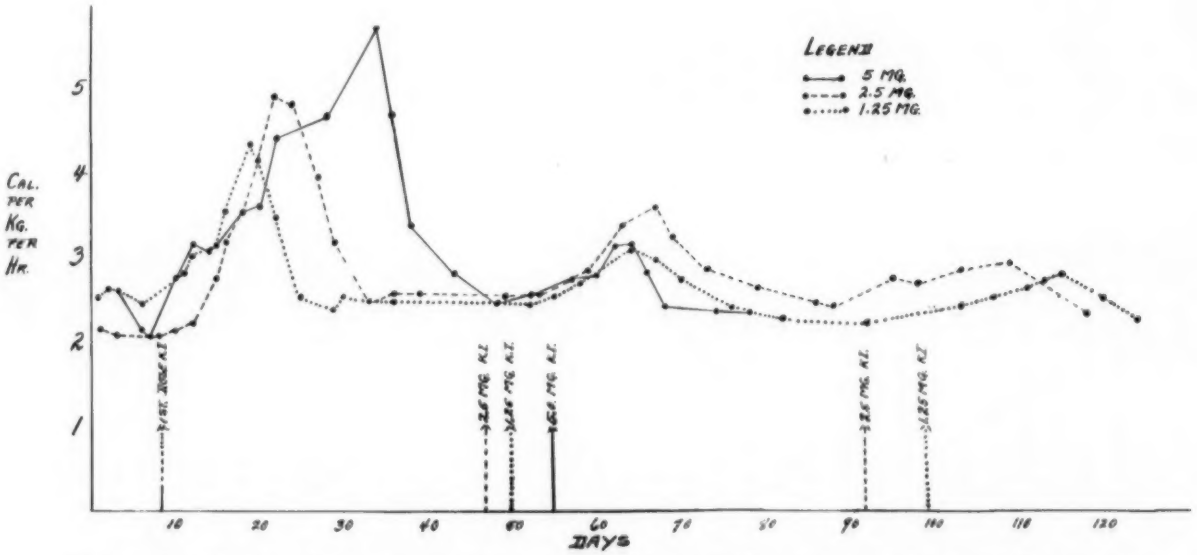


CHART II. THE EFFECT OF THREE DIFFERENT QUANTITIES OF KI ON THE HEAT PRODUCTION OF THREE RABBITS WITH THYROID GLANDS OF APPROXIMATELY THE SAME SIZE

produced by the same quantity of iodine, are reasonably constant in the different animals. On the fifty-seventh day of the experiment, or forty-one days after the first injection, when the level of metabolism had again become stabilized, a second biopsy was performed and the animals were again injected with 1.25 mgm. of potassium iodide, as shown on the chart. This time the metabolism did not rise to as high a level as it did after the first injection. The reaction however was of much shorter duration than in the first instance. At approximately the ninetieth day after the experiment was begun, a third biopsy was performed and shortly after, the animals were again injected with 1.25 mgm. of potassium iodide. In this instance the injections were not made on the same date, as indicated by the chart. The maximum rise was still less on this occasion. In brief, as Chart I shows, each successive dose of the same amount of potassium iodide resulted in a smaller rise in heat production. These reactions were constant in different animals with hyperplastic thyroid glands of approximately the same size.

Chart II illustrates the effect of various amounts of potassium iodide on the heat production of animals with thyroid glands exhibiting approximately the same degree of hyperplasia. The curves have been so transposed that the injection of the first dose of potassium iodide in all three animals occurs at the same period. It may be seen that 5 mgm. of potassium iodide caused the heat production to rise to more than twice its normal level. The peak was reached after approximately twenty-five days and the metabolic rate did not become stabilized until the fortieth day. At this stage a second biopsy was performed, and, on the forty-seventh day after the first injection, a second one of 5 mgm. was given. The rise in heat production was much less marked on this occasion. The peak occurred from seven to nine days after the injection and the maximum level was only 3.125 calories per kilogram per hour. The return to a basic level was rapid, occurring approximately thirteen days after the second injection. The explanation for this is suggested in the microscopic picture found in the biopsy which was performed on the seventy-eighth day of the experiment. This will be discussed later. The animal died from an excess of ether anesthetic on the seventy-eighth day of the experiment. The broken line represents the changes in metabolism produced by 2.5

PROTOCOL 1

Rabbit 2080

DATE	BODY WEIGHT	R.Q.	TOTAL CALORIES PER 2-HOUR PERIOD	CALORIES PER KILOGRAM PER HOUR
December 30, 1928	Biopsy thyroid gland (estimated weight 10 grams)			
January 3, 1929	2383.60	0.899	11.805	2.481
January 7, 1929	2389.20	0.883	12.005	2.512
January 11, 1929	2360.00	0.984	11.425	2.420
January 16, 1929	1.25 mgm. K I intraperitoneally			
January 18, 1929	2470.40	1.000	13.954	2.824
January 19, 1929	2282.00	0.803	13.650	3.000
January 22, 1929	2120.35	0.700	13.284	3.130
January 23, 1929	2060.00	0.752	14.596	3.542
January 26, 1929	1678.05	0.894	14.538	4.330
January 29, 1929	2187.01	0.953	15.179	3.470
February 1, 1929	1976.04	0.788	9.889	2.500
February 5, 1929	2160.05	0.820	10.589	2.358
February 6, 1929	2348.01	0.916	11.424	2.550
February 12, 1929	2241.06	0.744	10.025	2.460
February 18, 1929	2360.05	0.969	12.625	2.720
February 26, 1929	Biopsy thyroid gland			
February 26, 1929	1.25 mgm. K I intraperitoneally			
February 28, 1929	2297.04	1.000	10.951	2.400
March 3, 1929	2260.00	0.890	11.325	2.510
March 6, 1929	2203.01	0.950	11.864	2.698
March 12, 1929	2100.05	0.844	13.000	3.090
March 15, 1929	2150.04	0.802	12.604	2.931
March 18, 1929	2124.00	0.706	11.316	2.669
March 24, 1929	2300.05	0.904	11.025	2.390
March 30, 1929	2240.00	0.802	10.214	2.280
April 10, 1929	Biopsy thyroid gland			
April 16, 1929	1.25 mgm. K I intraperitoneally			
April 20, 1929	2294.10	0.876	10.956	2.403
April 24, 1929	2116.05	0.981	10.546	2.505
April 28, 1929	2205.10	0.846	11.662	2.620
May 1, 1929	2105.01	0.922	11.603	2.760
May 6, 1929	2210.10	0.840	11.005	2.498
May 10, 1929	2300.50	0.866	10.460	2.273
May 14, 1929	Biopsy thyroid gland			

mgm. of potassium iodide. Here it may be seen that the maximum rise was smaller than after 5 mgm. and was sustained for a much

shorter period. The rise after the second injection was higher than that in the case of the animal receiving 5 mgm., although it did not approach the level produced by the first injection. The change pro-

PROTOCOL 2

Rabbit 1832

DATE	BODY WEIGHT	R.Q.	TOTAL CALORIES PER 2-HOUR PERIOD	CALORIES PER KILOGRAM PER HOUR
November 25, 1928	Biopsy thyroid gland (estimated weight 10 grams)			
November 30, 1928	2338.50	0.884	13.548	2.890
December 3, 1928	2495.75	0.899	13.097	2.630
December 6, 1928	2444.00	0.830	10.396	2.125
December 7, 1928	2441.30	0.920	10.084	2.066
December 9, 1928	5 mgm. K I intraperitoneally			
December 10, 1928	2297.00	0.894	12.721	2.770
December 12, 1928	2502.70	0.912	15.790	3.158
December 14, 1928	2441.70	1.000	14.838	3.040
December 18, 1928	2208.10	0.757	15.467	3.515
December 20, 1928	2221.00	0.928	16.318	3.680
December 22, 1928	2111.50	0.740	18.695	4.428
December 28, 1928	2226.00	0.760	20.840	4.690
January 3, 1929	2322.00	0.843	26.650	5.750
January 5, 1929	2200.10	0.860	20.680	4.700
January 7, 1929	2154.25	0.926	14.582	3.390
January 12, 1929	2284.00	0.900	12.760	2.790
January 17, 1929	2250.00	0.992	11.099	2.466
January 21, 1929	2211.40	0.943	11.139	2.520
January 24, 1929	Biopsy thyroid gland			
January 24, 1929	5 mgm. K I intraperitoneally			
January 26, 1929	2213.00	0.920	12.043	2.720
January 29, 1929	2118.00	0.874	11.802	2.785
January 31, 1929	2270.00	0.960	14.167	3.120
February 2, 1929	2268.00	1.000	14.131	3.125
February 6, 1929	2286.00	0.979	10.720	2.340
February 12, 1929	2273.00	0.772	10.671	2.345
February 16, 1929	2462.00	0.940	11.325	2.300
February 19, 1929	Death from anesthetic during biopsy			

duced by the third injection on the ninety-second day of the experiment was considerably lower than that produced by the second. After the injection of 1.25 mgm. the increase in heat production

PROTOCOL 3

Rabbit 2040

DATE	BODY WEIGHT	R.Q.	TOTAL CALORIES PER 2-HOUR PERIOD	CALORIES PER KILOGRAM PER HOUR
December 28, 1928	Biopsy thyroid gland (estimated weight 9 grams)			
January 2, 1929	2640.00	0.741	17.040	3.227
January 3, 1929	2667.40	0.700	16.870	3.160
January 6, 1929	2625.55	0.951	11.340	2.156
January 10, 1929	2560.30	0.785	10.353	2.022
January 15, 1929	2551.00	0.804	10.400	2.035
January 16, 1929	2.5 mgm. K I intraperitoneally			
January 17, 1929	2459.05	0.727	10.229	2.081
January 19, 1929	2390.07	0.784	10.531	2.203
January 22, 1929	2207.70	0.707	12.136	2.758
January 23, 1929	2177.00	0.700	13.940	3.200
January 27, 1929	2051.60	0.918	17.144	4.180
February 1, 1929	2045.05	0.862	20.133	4.920
February 3, 1929	2050.04	0.846	19.743	4.810
February 6, 1929	2185.00	0.969	17.359	3.950
February 8, 1929	2034.05	0.815	12.802	3.153
February 12, 1929	2279.04	1.000	11.305	2.470
February 15, 1929	2040.10	0.785	10.363	2.540
February 18, 1929	2097.01	0.773	10.671	2.550
February 19, 1929	Biopsy thyroid gland			
February 26, 1929	2.5 mgm. K I intraperitoneally			
February 28, 1919	2030.04	0.805	10.205	2.510
March 4, 1929	1828.00	0.727	9.404	2.570
March 10, 1929	1978.00	0.880	11.319	2.861
March 14, 1929	2215.00	0.918	14.027	3.390
March 18, 1929	2040.05	0.839	14.598	3.570
March 20, 1929	2100.50	0.840	13.503	3.215
March 24, 1929	2080.10	0.866	11.865	2.870
March 30, 1929	2110.10	0.817	10.976	2.605
April 6, 1929	2056.04	0.763	9.979	2.430
April 9, 1929	Biopsy thyroid gland			
April 12, 1929	2.5 mgm. K I intraperitoneally			
April 15, 1929	2040.00	0.700	11.152	2.720
April 20, 1929	2100.51	0.840	11.158	2.653
April 25, 1929	1900.50	0.820	11.203	2.851
May 1, 1929	1870.01	0.840	11.033	2.950
May 5, 1929	2000.50	0.960	10.920	2.730
May 10, 1929	2201.05	0.884	10.252	2.330
May 12, 1929	Biopsy thyroid gland			

was lower than after either of the other two quantities and was sustained for a shorter period. Since the second injections were of necessity made at different intervals, the curves do not coincide after that point. The variations in these reactions may be explained, in part at least, by the changes in the histological picture of the glands as shown by the correlated series of biopsies.

An attempt was made to study the effect of the same quantities of potassium iodide used in the above experiments on the metabolism of rabbits with thyroid glands of a larger size. The animals available for this comparison possessed thyroid glands whose estimated weight varied from 15 to 18 grams. It would have been better, for purposes of comparison, if animals with larger glands had been available, but unfortunately, such was not the case. No definite difference in the reactions of the two series could be determined. The maximum increase in heat production, after the administration of iodine, was no greater in the case of the larger glands, although it appeared to be sustained for a longer period. Before definite conclusions can be drawn in regard to this point, however, it will be necessary to study the reaction in animals with considerably greater variation in the size of the thyroid glands than we were able to obtain.

RESULTS—HISTOLOGICAL

The changes in metabolism produced by the different quantities of iodine appear to coincide with the histological changes as shown by the various biopsies. At the preliminary biopsy, taken at the beginning of the experiment, almost identically the same type of gland was encountered in each of the animals studied. Grossly the thyroid glands were enlarged to many times the normal size and were bright red in color. The superficial vessels were greatly dilated and the whole structure bled very freely on the least injury. There was almost complete absence of colloid. The vascularity was prominent. The alveolar epithelium was columnar in type while the lumina were often ill-defined or absent. The so-called "chief" cell of Langendorff (7) was the predominating type. Only an occasional "colloid" cell could be found. Figure 1 is from the preliminary biopsy from rabbit 2080, (Protocol 1), and is typical of the glands as they were at the beginning of the experiment. The injection of a single dose of 1.25 mgm. of

potassium iodide produced striking changes in the gross and histological picture of the gland. On direct exposure at the second biopsy the thyroid was no longer found to be bright red but was reddish brown in color. The reduction in size was very marked, as was the decrease in vascularity. Pieces of tissue could now be readily taken from the gland without excessive bleeding. Figure 2 is from the same gland thirty-three days after the injection of 1.25 mgm. of potassium iodide. It shows that considerable colloid has been laid down. There is a reduction in the height of the alveolar epithelium and a definite decrease in vascularity. The "chief" cell is still the predominating type but there has apparently been an increase in the number of "colloid" cells. Figure 3 is from the same animal after the injection of a second dose of 1.25 mgm. of potassium iodide. The progress toward involution is even greater here. In amount the colloid is increased and is now somewhat unevenly laid down. The lumina are well defined and the alveolar epithelium is cuboidal in type. The number of "colloid" cells is still further increased and the nuclei of the "chief" cells appear to be more condensed and pycnotic in character.

Figure 4 shows the extent of involution produced by a single dose of 5 mgm. of potassium iodide. Here, too, the gross appearance was changed from a large, reddish, vascular mass of tissue to a red-brown, firm, almost normal-looking gland. The section shows that considerable colloid has been laid down and the height of the alveolar epithelium has been appreciably reduced. The changes in the nuclei of the alveolar cells noted above are even more marked here. Figure 5 shows the same gland at the third biopsy, twenty-six days after a second injection of 5 mgm. of potassium iodide. Here involution is practically complete. Figures 6 and 7 show the effect of the first and second injection of 2.5 mgm. of potassium iodide, respectively. It can be seen that the degree of involution is midway between the effect produced by the 5 mgm. and the 1.25 mgm. quantities of potassium iodide.

To summarize, the sections show a greater degree of involution after larger doses of potassium iodide than after smaller doses, and the metabolic studies likewise reveal a greater increase in heat production following the administration of larger doses. Comparison of the accompanying microphotographs with charts I and II indicates that the degree of heat production following successive doses of potassium

iodide can be closely correlated with the extent to which involution has progressed in the gland.

DISCUSSION

The experiments outlined above appear to have a bearing on the question of the relationship of available iodine to the output of thyroid hormone. The clinical observation that the administration of iodine to subjects with simple goitre increases the metabolism has been made on several occasions. Marine (8) in 1909 noted a loss in body weight

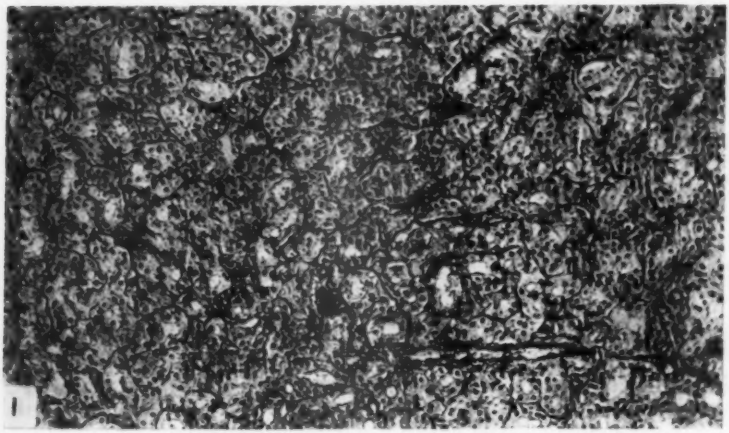
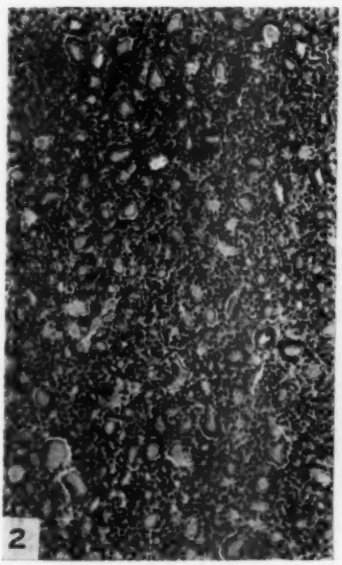


FIG. 1. SECTION TAKEN AT PRELIMINARY BIOPSY (RABBIT 2080), SHOWING HYPERPLASTIC CONDITION OF GLAND AT BEGINNING OF EXPERIMENT (× 100)

in goitrous dogs after the feeding of iodine. Webster and Chesney (1) have studied the metabolism of rabbits with simple goitre and found that there was a marked increase in heat production, often terminating in death, after feeding relatively large quantities of iodine. Kocher (9), Stiner (10), Silberschmidt (11), Bircher (12), Hartsock (13) Jackson (14) and others have reported instances of hyperthyroidism following the administration of iodine to patients with simple goitre. The results reported in the present communication suggest that the increase in metabolism obtained when iodine

was administered to animals with hyperplastic thyroid glands was dependent, within certain limits, on the amount of iodine supplied. Further, these experiments suggest that, while storage of iodine in the gland may take place soon after its administration, the elaboration of it into physiologically active hormone is much slower. They indicate that the presence of iodine is essential for the physiological activ-



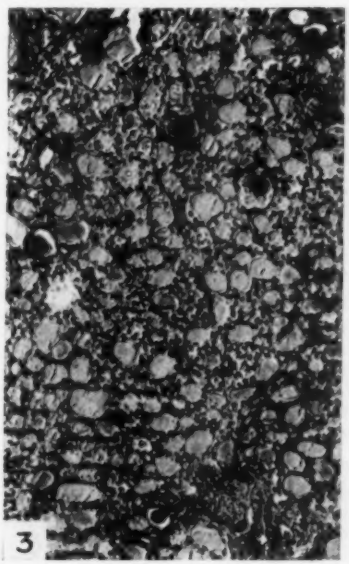


FIG. 2. SECTION TAKEN THIRTY-THREE DAYS AFTER A SINGLE INJECTION OF 1.25 MGM. OF KI (RABBIT 2080) (× 100)

FIG. 3. SECTION TAKEN AFTER THE SECOND INJECTION OF 1.25 MGM. KI (RABBIT 2080) (× 100)

ity of the hormone, and that the manufacture of physiologically active hormone is to some extent dependent on the quantity of iodine available. It would seem that the thyroid glands of these goitrous rabbits had reached the point where they were prepared to elaborate large amounts of hormone but were unable to do so because of the lack of something essential for its manufacture. The administration of iodine appeared to make up this deficiency, for after its exhibition, an

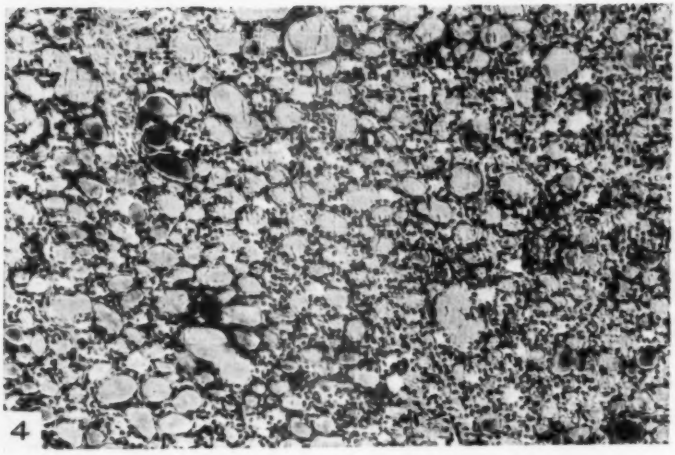


FIG. 4. FROM RABBIT 1832 (× 100) SHOWING THE EFFECT OF A SINGLE INJECTION OF 5 MGM. OF KI

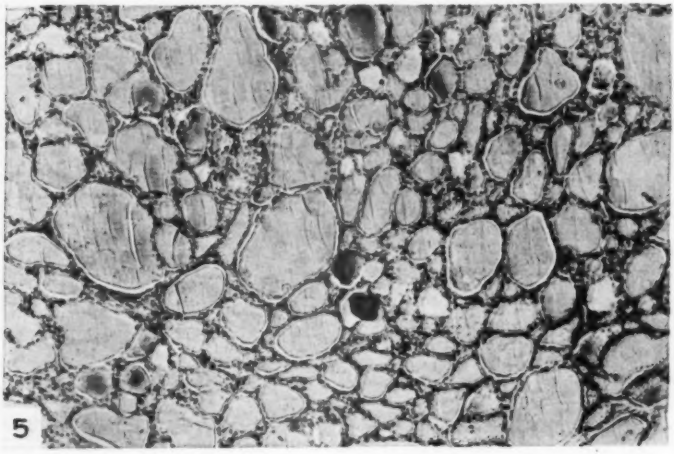


FIG. 5. FROM RABBIT 1832 (× 100) SHOWING ALMOST COMPLETE INVOLUTION AFTER A SECOND INJECTION OF 5 MGM. OF KI

FIG. 6. FROM RABBIT 2040 (× 100) SHOWING THE EFFECT OF A SINGLE INJECTION OF 2.5 MGM. OF KI

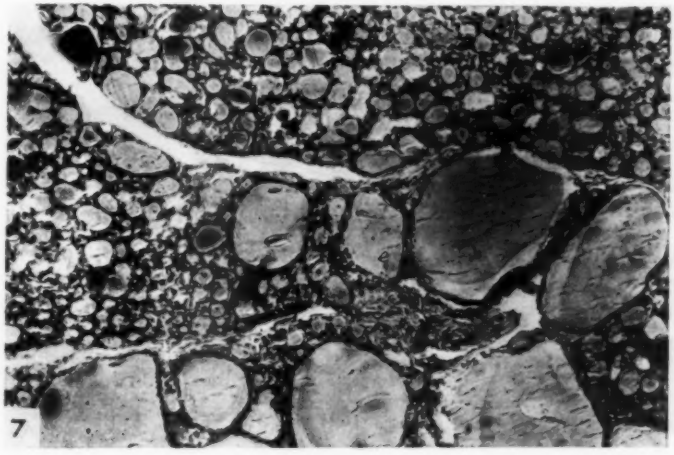


FIG. 7 FROM RABBIT 2040 (× 100) SHOWING THE EFFECT OF A SECOND INJECTION OF 2.5 MGM. OF KI

Note irregular distribution of colloid

increase in heat production occurred and the glands began to involute. One can conceive of the hyperplastic glands being able to synthesize and store up a hypothetical substance which needed only the addition of iodine to change it into the physiologically active hormone. The experiments herein reported coincide with this conception. The experiments of Gaddum, (15) in which he has shown that desiodothyroxin (*i.e.*, synthetic thyroxin without the addition of the 4 iodine atoms) has no effect on the metamorphosis of amphibian larvae, also favour this hypothesis. The observations in the present investigation suggest also that the manufacture of the hormone may proceed, in an iodine deficient gland, to the stage of the organic portion of the molecule (desiodothyroxin or some similar compound). This apparently remains inactive until iodine is supplied to complete the molecule and create a physiologically active hormone. The difference in the metabolic reaction to iodine of rabbits with normal thyroid glands and those with simple goitres (1) suggests that this inactive form of hormone is present in a greater amount in the simple hyperplastic conditions of the gland than in the normal thyroid. Further, the gradual rise and fall of the metabolism after the administration of iodine, as noted in the present investigation, may indicate some controlling mechanism which regulates the manufacture or liberation of active hormone, even in the presence of a sufficiency of iodine.

The histological changes noted in the thyroid glands following the injection of iodine, revealed an increasing tendency toward involution with increase in the quantity of available iodine, just as did the increase in heat production. The failure of the partially involuted glands to give as active a metabolic response to iodine, as did the more hyperplastic ones, can perhaps be accounted for on the basis of absorption, since Marine and Rogoff (3) have shown that the quantity of iodine absorbed depends on the degree of hyperplasia of the gland.

There was apparently some increase in the number of "colloid" cells in the acinar epithelium after the administration of iodine. Further, there appeared to be a progressive tendency for the nuclei of the "chief" cells to approach those of the "colloid" ones in type. This suggests a relationship between the functional activity of the gland and the kind of cell making up the alveolar epithelium.

SUMMARY

Potassium iodide in quantities of 5, 2.5 and 1.25 mgm. was injected intraperitoneally into rabbits with simple hyperplastic thyroid glands and the changes in heat production were studied and correlated with the histological changes produced in the gland, as determined by biopsy. The quantity of thyroid hormone elaborated, as indicated by changes in heat production, appeared to vary directly, within certain limits, with the amount of available iodine, as did the extent of involution produced in the gland. This relationship apparently held true until involution was nearly complete.

The author wishes to acknowledge his indebtedness to Dr. Alan M. Chesney and to Dr. David Marine for many helpful suggestions.

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THE RETINAL BLOOD VESSELS IN HYPERTENSION AND ARTERIOSCLEROSIS

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From the earliest days of ophthalmoscopy onwards the effort has been made both by ophthalmologists and by internists to correlate the various fundal pictures with constitutional disorders. In relation to those retinal lesions that result primarily from diseases of the blood vessels the investigation has gone through several stages, each of which has contributed important facts to our knowledge. At first, interest was directed mainly toward the more dramatic features of the ophthalmoscopic picture,—hemorrhages and "exudates," spots of various form and color,—and the different types of "retinitis," diabetic, albuminuric, arteriosclerotic, and others, were described, together with the more aberrant and unusual forms, such as retinitis circinata, retinitis punctata centralis, and central senile chorioretinitis. These retinitides were found to occur so frequently in typical form as to warrant the hope that some special constitutional condition might be discovered which could be related causally to each retinal picture. Extensive clinical studies were, therefore, made and in some instances fairly close correlation has been established, sufficient to justify the adoption of such names as "albuminuric retinitis" or "diabetic retinitis."

Even in these chosen instances, however, the correlation has been far from satisfactory. Cases which were ophthalmoscopically indistinguishable from "albuminuric retinitis" were found in individuals who had no renal disease, and innumerable instances of advanced chronic nephritis were seen in which the ophthalmoscopic picture did not resemble the typical form of albuminuric retinitis. These

[1] Read in summary before the Johns Hopkins Medical Society, November 7, 1927.

[2] Submitted for publication December 15, 1928.

findings have led to the realization that the retinal hemorrhages and "exudates"—we use the quotation marks because most of the white spots seen with the ophthalmoscope are not, in fact, exudates but serous transudates and hyalin, colloid, or lipoid deposits—were to be considered as phenomena of secondary and accidental origin, dependent in largest measure upon local vascular disease and local anatomical peculiarities.

With the realization of the fundamental importance of retinal vascular lesions a new set of investigations was instituted by many workers who reversed the earlier attack on the problem. Instead of asking what constitutional condition is most often associated with a given eye-ground picture, they inquired how often and in what degree does retinal arteriosclerosis occur in such diseases as chronic nephritis, hypertension, diabetes, and other conditions. Such investigations defined more clearly the ophthalmoscopic appearance of retinal vascular disease and disclosed the close parallelism which exists between general arteriosclerosis and retinal arteriosclerosis. This conclusion, while perhaps the most definite and certain that can be drawn in this whole domain, is still very unsatisfactory, for neither does retinal, nor does general arteriosclerosis constitute a single disease picture. One cannot but wonder whether the form and distribution of the retinal vascular lesions might not be closely related to the form and distribution of the associated general vascular disease and to its clinical manifestations. Among the problems which are suggested by this line of reasoning, the special questions which have, in the past, received most attention are the following:

(1) What are the retinal signs of vascular hypertension? (2) Does arteriosclerosis, as evidenced in the eye-ground, precede or follow the development of hypertension? In answer to the first, numerous writers have asserted that the primary retinal signs of hypertension are arteriovenous compression and changes in the light streak over the arteries, the latter being described somewhat differently by different authors. Since our own observations are not entirely in accord with these statements it may be well to present the evidence both pro and con at this point.

It is undoubtedly true that arteriovenous compression is very often seen in hypertensives. Extreme grades such as are pictured in

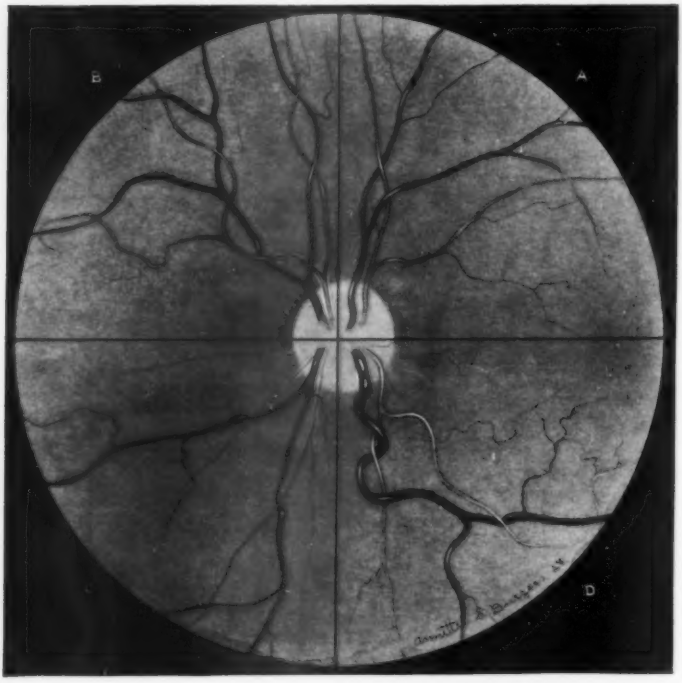

FIG. 1. COMPOSITE DRAWING ILLUSTRATING VARIOUS TYPES OF RETINAL VASCULAR LESIONS

A. *Normal.* B. *Senile arteriosclerosis without hypertension.* The larger arterial branches show leading and visibility of their walls. There is moderate arterio-venous compression. The general calibre of the arteries, however, is normal, and the arterioles show no lesions. C. *Arteriosclerosis with hypertension.* There is a general reduction in calibre of the whole arterial tree. In addition, the arteries are straight, they branch at an acute angle, they show fine calibre variations (beading), increased visibility of their walls, disappearance of the reflex stripe. There is marked arterio-venous compression. D. *Arteriolar sclerosis.* The larger arteries are full and tortuous, coppery in appearance with a widening of the reflex stripe. Moderate arterio-venous compression is present. The arteries branch at right angles. The terminal arterioles show irregular tortuosity, fine caliber variations, visibility of their walls, silver wire change.

Sections C and D of the accompanying illustration are rarely found except in cases of long standing and severe hypertension. In such instances, however, the compression persists when, as a result of some intercurrent disease, the blood pressure falls to normal levels. The arteriovenous compression in these extreme cases must result, therefore, from some structural change in the vessel wall rather than from the intra-arterial pressure. The results of histological studies on this and other problems dealt with in this paper will be given in a separate communication. We wish to confine ourselves here to the purely clinical aspects of the subject. Setting aside the question of the physical mechanism of venous compression, but admitting that it results from, or is accompanied by, structural changes in the vessel walls, one can still not be certain that hypertension is the primary cause. Instances are seen, truly not very often, of extreme grades of arteriovenous compression in elderly persons with advanced arteriosclerosis without hypertension. One cannot, of course, be sure that these individuals have never had hypertension, but they often show no evidence, either in renal damage or in cardiac hypertrophy, of having had such trouble.

A stronger argument for the relation between hypertension and arteriovenous compression can be made in regard to those cases in which the compression is of lesser degree. Instances of this kind are seen at times quite early in hypertension. Indeed, when the hypertension is transitory, as in acute nephritis, the compression may disappear when the pressure returns to normal or, at most, a few weeks later. Bardsley (1) has observed transitory venous compression in hypertension artificially induced by adrenalin injection. On the other hand, mild grades of compression of this sort are seen not infrequently in perfectly normal persons, and the diagnosis of hypertension on this sign alone, is, as we have found, subject to frequent error.

In regard to changes in the arterial reflex, the authors who are agreed that such changes are pathognomonic of hypertension are not agreed as to the nature of the changes. Some point to increased brightness and sharper definition of the reflex, while others state that it is broader and associated with a softer, more coppery appearance of the vessel. Finally, others have noted irregularity in the course and width of the reflex. In part these differences may have resulted from

differences in the type of ophthalmoscope used by different observers, for the reflex, as was long ago pointed out by Dimmer (2), is actually an optical image of the illuminated portion of the patient's pupil formed by reflection from the convex cylindrical surface of the vessel wall or blood column. The form of the reflex will vary, therefore, not merely with changes in the blood vessel which affect the diameter and smoothness of the reflecting surface and the transparency of the overlying tissues, but also with the size of the pupil and with the construction of the ophthalmoscope used.

Our own observations on the arterial reflex have led us to the following conclusions: When the same ophthalmoscope is used and when the pupil of the observed eye is of approximately constant size, the width of the arterial reflex is most closely related to the width of the blood column. Instances in which the band is abnormally wide are generally associated with a coppery color of the arteries and are found especially in relation to the larger arteries in cases of retinal arteriolar sclerosis such as is shown in Section D of the figure. Irregularity of the arterial reflex is associated with fine irregularities in the calibre of the vessels—the so-called beading. Increased brightness of the reflex occurs commonly in darkly pigmented fundi and appears to us to be without clinical significance. In cases with markedly attenuated arteries the reflex may practically disappear.

The more fundamental problem as to whether arteriosclerosis precedes or follows hypertension has engaged the attention of many workers, several of whom have attempted to use the eye-ground picture as a criterion of early sclerotic changes. The results have been inconclusive. Broadly stated, the facts are as follows: Advanced cases of hypertensive disease almost always show retinal vascular lesions; early mild cases almost always show normal fundi. In general, therefore, retinal arteriosclerosis may be said to follow hypertension. It must be observed, however, that there are two important exceptions to this statement: (*a*) Cases are seen in which hypertension has existed for many years without visible change in the retinal arteries. These include cases of essential hypertension, and also, as Altnow (3) has recently shown, cases of hyperthyroidism with high systolic blood pressure levels. Furthermore, the time of onset and the severity of the retinal vascular lesions do not seem, in many

instances, to be intimately related to the duration and severity of the associated hypertension. We shall endeavor to show how some of these apparent contradictions may be resolved. (*b*) The second exception to the statement that retinal arteriosclerosis follows hypertension is found in a group of cases with quite outspoken retinal and also peripheral vascular lesions in which the blood pressure is normal. In

TABLE I

Elements in the ophthalmoscopic picture to which attention was directed

1. Calibre of the arteries.
   a, Normal; b, dilated; c, contracted; d, fine calibre variations.
2. Visibility of the vessel walls.
   a, Normal (invisible); b, faintly visible; c, well marked white streaks beside the blood column; d, silver-wire change.
3. Arteriovenous compression.
   a, Absent; b, slight; c, moderate; d, extreme.
4. Arterial reflex.
   a, Normal; b, irregular; c, widened (copper-wire change); d, absent.
5. Distribution of the vascular lesion.
   a, Main branches of the retinal artery; b, terminal arterioles in the macular region and periphery of the fundus; c, scattered.
6. Hemorrhages, exudates, and oedema.
   a, Character; b, distribution (central or peripheral).
7. Evidences of choroidal arteriosclerosis.
   a, Exaggerated tigroid appearance; b, colloid excrescences; c, subretinal hemorrhages; d, pigmentary irregularities; e, central senile chorioretinitis.

Note. We wish to emphasize especially the importance of a careful examination of the macular arterioles. With a good opbthalmoscope and a clear eye it is possible to see in this region vessels whose internal diameter is of the order of 10 to 15 microns. Vessels of this size are nowhere else in the body susceptible to direct clinical examination. In some cases of vascular disease of the most serious type these vessels are the only ones in the retina which show marked lesions.

some of these cases evidence is found of some intercurrent disease which can account for the lowering of the blood pressure which may previously have been quite high; but in other cases the absence of cardiac hypertrophy and of renal damage supports the view that severe hypertension has never existed. It may be supposed that the character and distribution of the vascular lesion in these cases is somewhat different from that which is associated with hypertension, and this is a thesis which we shall maintain below.

TABLE II

CLINICAL TYPE	COMMENT	DOMINANT FEATURES IN EYE-GROUND	ACCESSORY EYE-GROUND FINDINGS	EXCEPTIONS	
				A. Clinical features present with absent or atypical eye-ground findings	B. Typical eye-grounds with atypical clinical findings
I. Hypertension without retinal arteriosclerosis	Acute nephritis, essential hypertension, *Stauungshypertonie*, pregnancy, brain tumor, hyperthyroidism, etc.	Normal; or slight arteriovenous compression	Slight oedema of retina sometimes seen in acute nephritis	a. Cases of toxaemia of pregnancy with eye-ground picture of albuminuric retinitis b. Similar rare cases of acute nephritis	Mild grades of arteriovenous compression often found in healthy young persons
II. Retinal arteriolar-sclerosis	Especially in rapidly progressing chronic nephritis. The eye-grounds reveal no distinctions between arteriolar sclerotic nephritis and chronic glomerulo-nephritis	Larger vessels full and tortuous. Arteriovenous compression. Irregular tortuosity, calibre variations, visibility of the walls of small macular arterioles and of those in periphery of fundus. Fig. 1, Section D	Typical picture of albuminuric retinitis is often seen in these cases. In late stages larger arteries also show sclerotic changes	a. Cases of rapidly progressing chronic nephritis with predominant arterial rather than arteriolar retinal lesion, most often seen in women b. Arteriolar changes sometimes not visible in macula in albuminuric retinitis on account of oedema, but visible in periphery of fundus	Cases of retinal arteriolar sclerosis sometimes seen before development of renal signs
III. Retinal arteriosclerosis with hypertension	Especially in elderly persons, but seen also at times in younger people. Prognosis worse in younger individuals. Renal damage is quite variable, often slight	Diffuse constriction of larger arteries with fine calibre variations, arteriovenous compression, disappearance of reflex stripe. Fig. 1, Section C.	Visible thickening of walls of arteries and veins. Thrombosis of large branches. Scattered hemorrhages and exudates. Choroidal arteriosclerosis	Early and mild cases sometimes fail to show arterial constriction	Typical eye-ground findings with low or normal blood pressure. These cases reveal with a high degree of uniformity some cause for low blood pressure, such as cardiac failure, malignancy or other intercurrent disease

IV. Retinal arteriosclerosis without hypertension	Senile cases. No cardiac hypertrophy	Differ from Group III in that the larger vessels are of normal calibre. Arterioles normal. Fig.1, Section B	Beading of larger vessels, irregularity in light streak, visible walls, arteriovenous compression (rare); hemorrhages, exudates (scattered); choroidal arteriosclerosis		In young and middle-aged individuals the same picture is usually associated with hypertension. As these cases progress the picture usually changes to that noted in Group II or III
V. Syphilitic arteriosclerosis	Sometimes seen in CNS syphilis, almost never in tabes or paresis	Lesions when present are at times widely scattered, some vessels appear normal, others markedly sclerotic			
VI. Retinal arteriosclerosis resulting from local disease	Optic atrophy, glaucoma, retinitis pigmentosa, local inflammatory disease, etc.	Extreme narrowing of arteries *and veins*, calibre variations, visible walls. Arteriovenous compression (rare)	Perivascular scarring from the organization of inflammatory exudates		When general arteriosclerosis is present in addition, it is often difficult to evaluate how much of the retinal vascular lesion is due to antecedent local cause and how much to constitutional factors

In view of the accepted theories as to the mechanics of hypertension it has been natural to hope that, apart from sclerotic changes, some evidence of arterial spasm might be found in the eye-grounds in cases of hypertension. No such evidence has, however, been forthcoming. This does not prove the absence of arterial spasm in other organs. Florey (4) has shown that the vasomotor control in the brain differs radically from that in the viscera. The absence of retinal arterial spasm in hypertension may be taken to indicate that the vasomotor control in the retina resembles that in the brain.

Such, in summary, is the present status of this subject. The diagnostic and prognostic significance of the various forms of retinal hemorrhages and exudates are known within rather wide limits. The dependence of these hemorrhages and exudates upon retinal vascular lesions can hardly be questioned. The close association between retinal and general arteriosclerosis is well established, but the types of retinal vascular lesions have been only incompletely differentiated. The present study is an effort to pick out from the protean features of retinal vascular disease certain dominant elements, and to establish, if possible, the diagnostic and prognostic significance of these elements.

In order to attack the problem *de novo* and to subject to a rigid objective analysis those preconceptions which one can only with difficulty eliminate from the consideration of a subject of this kind, cases were examined without any prior knowledge of the general physical condition. The character and distribution of the retinal lesions were noted in accordance with the outline in Table I. An estimate of the patient's vascular status was then made and compared with the actual clinical findings. In this way various hypotheses could be tried out in rapid succession. For example, our attention was first directed toward the question of the relation of arteriovenous compression to hypertension. The results of this part of the study have already been stated.

The data which we are presenting are based upon the examination of all admissions to the medical services at the University, the Mercy and the Sinai Hospitals over a period of several years, and also of a considerable number of cases on the medical service of the Johns Hopkins Hospital. We are indebted to the chiefs of these services for their coöperation in placing this material at our disposal. In all,

approximately 2000 cases were examined. Rather than present elaborate tables of our findings we shall give only a summary of our observations and conclusions.

GROUPING OF CASES

Early in the course of our studies it became apparent that cases of general vascular disease could be sorted into certain groups with respect to the ophthalmoscopic findings. While we realize the almost infinite series of gradations which are to be found between any arbitrarily chosen types, we feel that the classification which we have based essentially upon the eye-ground findings is not without clinical significance (see Table II).

I. Hypertension without retinal arteriosclerosis

Under this heading we include cases of great clinical diversity such as essential hypertension, acute nephritis, mild toxemias of pregnancy, increased intracranial pressure, cardiac decompensation with transitory hypertension (*Stauungshypertonie*), hyperthyroidism with high systolic pressure, etc.

In these cases the eye-grounds are normal or at most show slight arteriovenous compression. The venous compression is usually not of a degree beyond that occasionally seen in normal persons, but occurs with greater frequency in these cases than in normal individuals, and, as noted above, may disappear when the blood pressure has returned to normal. It is of special interest that individuals of advancing years with beginning hypertension usually show at the outset no retinal arteriosclerosis. This is particularly noteworthy of women in the climacteric period.

II. Retinal arteriolar sclerosis and albuminuric retinitis

The ophthalmoscopic picture which we interpret as retinal arteriolar sclerosis is illustrated in Figure 1, Section D. The characteristic features in these cases are localized variations in calibre, irregular tortuosity, and visibility of the walls of the terminal arterioles. The actual internal diameter of the vessels primarily involved in this process may be estimated at from 10 to 25 microns. These vessels can be studied best in the macular region, because the optical properties of

the eye give the best definition of the image in this region. In advanced cases, however, similar changes can be seen in vessels of the same order in the periphery of the fundus. In regard to the tortuosity of these vessels a distinction must be made between the irregular tortuosity characteristic of vascular disease and the smooth sinuous tortuosity which is often seen in congested fundi in fever, eye-strain, etc. The larger retinal arteries in early cases are full and tortuous and often show a widening of their reflex band associated with a coppery appearance of the blood column. Arteriovenous compression of marked grade is usually present and is seen at the points of crossing of both large and small branches. In late stages of this condition the larger arteries also show marked lesions such as beading, increased visibility of their walls, and even diffuse constriction of calibre. A point of distinction between these cases in their late stages and those of the group next to be described is that the larger arteries in arteriolar sclerosis usually remain tortuous and branch at right angles even when they have become greatly narrowed, while in the next group they are generally quite straight and branch at acute angles (Fig. 1, Section C).

In the series of cases which we examined an exceedingly close connection was found between retinal arteriolar sclerosis and albuminuric retinitis. All of the cases of retinal arteriolar sclerosis which we were able to follow over a sufficiently long period developed typical albuminuric retinitis and, furthermore, all of the cases of albuminuric retinitis which we studied showed arteriolar changes. Even in those cases in which the macular vessels were hidden from view by retinal oedema and exudates, similar arteriolar lesions were found in the periphery of the fundus. We may conclude, therefore, that retinal arteriolar sclerosis is closely connected with the etiology of albuminuric retinitis.

The clinical findings in the cases, both with and without albuminuric retinitis were of the same character and consisted in very marked hypertension, sooner or later associated with a rapidly progressing chronic nephritis. Indeed, all the well known facts regarding age incidence, clinical associations, and prognostic significance may be transferred bodily from the cases of albuminuric retinitis to the somewhat larger group of cases of retinal arteriolar sclerosis.

In view of the close association between retinal arteriosclerosis and general arteriosclerosis one is inclined to assume that in these cases arteriolar sclerosis of other organs is also present, but the proof of this must rest upon anatomical studies. From the purely clinical side the association does not appear to be invariable. On the one hand, we have seen many cases in which the history of long standing hypertension, headaches, etc., antedating urinary evidence of renal lesion, indicated an essentially arteriolar sclerotic process, but in which the eye-grounds showed lesions predominantly in the larger vessels. On the other hand, we have been unable to find any special signs in the eye-grounds of cases of retinal arteriolar sclerosis which would enable us to differentiate between those cases which were clinically diagnosed as general arteriolar sclerosis and those, equally often associated with typical retinal arteriolar lesions, which were clinically classified as glomerulo-nephritis.

III. Retinal arteriosclerosis with hypertension

In elderly persons with arteriosclerosis of a slowly progressing type associated with hypertension the eye-grounds showed most often the picture which is illustrated in Section C of the accompanying figure. The outstanding feature in these cases is the reduction in calibre of the whole arterial tree. The relation of the hypertension to the calibre of the main arterial branches in these cases is so close that the blood pressure can usually be estimated within quite narrow limits from the consideration of this sign alone. As a rough measure it may be said that when the arteries are reduced to approximately one-half their normal calibre (as in section C of the Figure) the diastolic blood pressure will be found to be 110 mm. or more. The exceptions to this rule are of two kinds: (*a*) early cases in which the blood pressure is often higher than is to be expected from the eye-ground picture and (*b*) cases in which some intercurrent disease has reduced the blood pressure which was previously high. Among these were found cases of cardiac decompensation, of malignancy, of acute infectious disease, and of chronic pulmonary infections. There were a few cases of this kind in which no constitutional cause for the reduction of blood pressure was found but in which one could still surmise that the normal, compensated blood pressure level was much higher than that actually

found. These individuals complained of vertigo, muscular weakness, lassitude, etc., and one such patient developed extensive cerebral thromboses while under observation. We have come, therefore, to view the finding of low or normal blood pressure with constricted retinal arteries in elderly people as of grave significance.

The ophthalmoscopic changes commonly associated with diffuse constriction of the larger arterial branches are numerous. Often the constriction extends to the smaller vessels which may become invisible. The arteries are usually quite straight and branch at acute angles. There is often arteriovenous compression of a considerable grade, and the lowering of the blood pressure through intercurrent disease exerts no apparent influence on this sign. In addition to the diffuse constriction of the arteries fine local variations in calibre are almost always seen, and with these are associated fine irregularities in the light streak. In extreme constriction of the arteries, however, the light streak may disappear entirely. In many cases there is an increased visibility of the vessel walls. Evidences of choroidal arteriosclerosis are also often present. Hemorrhages and white spots of various kinds occur commonly in advanced cases and are usually widely scattered throughout the fundus, rather than concentrated in the central regions as in arteriolar sclerosis and albuminuric retinitis. In those cases that have developed this ophthalmoscopic picture while under our observation, the hypertension has preceded the retinal arterial constriction.

As stated above, the ophthalmoscopic picture which we are describing occurs most frequently in elderly persons. Occasionally, however, similar lesions are seen in persons of middle age, and even in young individuals. In general, it seems, with this as with other arteriosclerotic manifestations, that the earlier the onset the more grave the prognosis. Indeed, this ophthalmoscopic picture was found in some cases of middle age with quite severe and rapidly progressing chronic nephritis. This combination was most often seen in women, a finding which is in accord with the fact that the prognosis of chronic nephritis and hypertension is somewhat better in women than in men, for in severe cases the latter more often show retinal arteriolar sclerosis.

It is interesting to note that the constriction of the retinal arteries

has been only rarely mentioned in the discussion of retinal arteriosclerosis. This may be because the condition is found so commonly among elderly persons as to have been considered within the range of normal variations.

IV. Retinal arteriosclerosis without hypertension

In some cases we have found a retinal picture in many ways resembling that just described, but with this difference,—the main arterial branches are full and tortuous. All the accessory findings such as arteriovenous compression, calibre variations, visibility of the vessel walls, choroidal arteriosclerosis, scattered hemorrhages and white spots may be present in varying degree as shown in Figure 1, Section B. Elderly persons presenting this ophthalmoscopic picture have, in general, shown no hypertension, no cardiac hypertrophy nor other evidence of previous hypertension, no symptoms which would suggest that the blood pressure had fallen below the normal compensated level, though signs of peripheral or visceral arteriosclerosis are generally to be found.

The prognosis in elderly persons, with arteriosclerosis but without hypertension, showing the ophthalmoscopic picture which we have described, is somewhat indeterminate; for the vascular lesion in these cases is prone to have a rather uneven distribution. In general, however, they show relatively little renal involvement. The same ophthalmoscopic picture, or at least one which we have been unable to differentiate from this, when found in younger persons, is usually associated with hypertension, and with a more grave prognosis. As these latter cases progressed, the retinal picture changed to one or the other of the preceding pictures (II or III, usually the latter).

V. Syphilitic arteriosclerosis

Most luetics with arteriosclerosis show nothing in their retinal vessels distinctive of syphilis. In a number of cases of central nervous system syphilis, however, it was noted that the retinal vascular lesions were peculiarly scattered, one arterial branch showing marked changes, while its neighbor appeared perfectly normal. A similar scattering of the vascular lesions is seen only rarely in non-syphilitic individuals. We feel, therefore, that this picture, while not pathogno-

monic of syphilis, is, nevertheless, quite suggestive. We were much struck by the fact that while this type of lesions was seen fairly often in central nervous system syphilis, it was not noted in any of the cases of tabes or paresis that came under our observation.

VI. Retinal arteriosclerosis resulting from local disease

The changes in the retinal blood vessels which accompany retinal atrophy resulting from local diseases such as optic atrophy, glaucoma, retinitis pigmentosa, etc. reveal few signs which are in themselves distinctive. The vessels often show beading and visible walls. In some cases the most extreme reduction of vascular calibre is reached, the veins, as well as the arteries, being affected. Arteriovenous compression is rare, but may occur. Hemorrhages and exudates are rarely seen with this type of lesion unless they are associated with antecedent local disease. Perivascular veils of connective tissue are often found in those cases in which the antecedent ocular disease has been of an inflammatory nature.

The differential diagnosis between general and local cause for retinal arteriosclerosis is usually made simple through the presence of other obvious signs of local disease, but in cases where both factors combine it is almost impossible to estimate how much of the damage is to be attributed to each.

SUMMARY AND CONCLUSIONS

From a study of the eye-grounds of approximately 2000 medical cases a working classification of retinal vascular disease has been formulated and the clinical correlations of each of the several types of lesions have been investigated. The classification is summarized in Table II.

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OBSERVATIONS ON THE DEGENERATION AND REGENERATION OF POST-GANGLIONIC NERVE FIBERS

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INTRODUCTION

Although the sympathetic nervous systems have been extensively and carefully studied by many investigators, there have been but a few published descriptions of the phenomena associated with the degeneration and regeneration of the post-ganglionic fibers. Since the post-ganglionic fibers of the cervical sympathetic chain have hardly been investigated since Langley took such great interest in the general subject of sympathetic nerves at the beginning of this century, it was hoped that some additional information might be obtained from the following series of experiments.

METHOD AND MATERIAL

Only cats were used throughout the entire series of eighty-four experiments. The left cervical post-ganglionic sympathetic nerve fibers were chosen since they were relatively easily dissected out and also because some of the changes following their section could be examined quantitatively (Lee).

All operations were performed aseptically under intra-tracheal ether anesthesia. In all cases the left cervical sympathetic nerve was exposed in the neck and traced to the superior cervical sympathetic ganglion which was separated from the vagus nerve and ganglion. The sympathetic nerve trunk was lifted up gently by means of a silk thread placed near the ganglion and the post-ganglionic fibers cut with a sharp scissors a few millimeters from the upper pole of the ganglion. In some cases the retraction of several millimeters between the sectioned ends was allowed to remain; in other cases, a fine silk suture of China beaded silk was used to bring the ends into juxtaposition. The needle employed for this purpose was very fine and

about three millimeters long; an attempt was made to pass the needle through the epineurium and to injure the nerve fibers as little as possible.

The subsequent histological studies were made from cross and longitudinal sections of the proximal and distal segments. The stains employed were osmic acid, iron hematoxylin and Van Gieson, hematoxylin and eosin, and a modification of Cuajunco's stain (Lee) for the axis-cylinders.

Immediately after the operation the nictitating membrane covered the cornea completely. Photographs were taken frequently, and sketches were made almost daily to indicate the position of this membrane in comparison with the one on the control side. The size of the pupils was also established routinely by the use of the millimeter scale; in addition, frequent photographs were taken. The temperature in the two ears was measured simultaneously by means of centigrade thermometers, around the bulbs of which the auricular appendage was held by means of a rubber-shod clamp. Other paralytic symptoms, such as increased lachrymal secretion, salivation, ptosis, enophthalmos and sneezing, were also noted (Pye-Smith, Langendorf, Langley).

It was soon evident that these signs of paralysis gradually disappeared and that the pupils became equal. But whether this recovery was due to regeneration could only be determined definitely by electrical stimulation of the nerve proximal to the lesion. Accordingly, as soon as the pupils became equal, the cat was again anesthetized and with aseptic precautions the pre-ganglionic nerve fibers on the side under consideration were isolated from the vagus nerve and stimulated with a weak faradic current. In every case such a stimulation at once gave a widening of the lid slits, retraction of the nictitating membrane, constriction of the ear vessels, and enlargement of the pupil. It was thus believed that regeneration had taken place at the point of section.

OBSERVATIONS

The signs of paralysis following this operative procedure were studied at first daily while the changes were still marked; later the examinations were made every other day. All the observations were made in the same room, at the same time of day, and with the same illumination.

Before detailing the changes during recovery from the paralysis, it may be well to describe some of the morphology of the structures under consideration (Müller). The number of rami or bundles given off from the anterior (superior) end of the ganglion varies. The superior cervical ganglion is a relatively large one, and is in close apposition to the ganglion nodosum of the vagus nerve to which it is connected by several small nerve fibers. From the anterior end of the superior

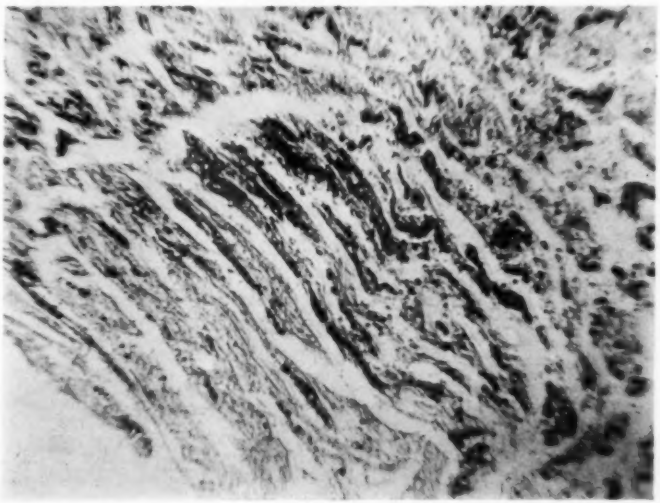

FIG. 1. OSMIC ACID STAIN, LONGITUDINAL SECTION, TO SHOW THE DISAPPEARANCE OF THE MYELIN SHEATH IN THE DISTAL SEGMENT SEVEN DAYS AFTER SECTION OF THE POST-GANGLIONIC FIBERS

cervical ganglion three or four nerve bundles pass cranially and are called the cranial bundles (Langley). Of these bundles there is always one, usually in the middle, which is larger than the others. About a millimeter from the anterior pole, a small strand of nerve fibers arises from each side; these fibers are spoken of as the dorsal and lateral bundles. From this dorsal bundle two or three divisions pass to the external carotid artery and are called the external carotid bundles. Other fibers coming from the cranial end of the ganglion

connect with cranial nerves emerging from the jugular foramen forming a plexus in this region. Still other fibers passing forward with the internal carotid artery and forming a plexus about it, continue to the Gasserian ganglion and unite with its ophthalmic branch. Subsequently, in the long ciliary branches they leave the ophthalmic nerve and terminate in the dilator muscle of the pupil. Obviously, when the path of these fibers is interrupted the pupil is seen to contract.

FIG. 2. MODIFIED CUAJUNCO STAIN. CROSS SECTION OF THE DISTAL (REGENERATED) SEGMENT OF POST-GANGLIONIC FIBERS NINETY DAYS AFTER OPERATION AND THIRTY-TWO DAYS AFTER REGENERATION HAD TAKEN PLACE
a, nerve bundles; *b*, individual axone

On the other hand, these nerves may be stimulated by emotional states such as fear, to produce a large pupil; and a similar condition may be produced by putting a weak solution of cocain into the conjunctival sac. Each eyelid contains, furthermore, a layer of unstriated muscle which is supplied by sympathetic nerves, and the ptosis following section of these nerves may be explained on this basis. The external carotid branches from the ganglion pass along the external

carotid artery and convey vaso-constrictor impulses throughout the course of this vessel. It has also been claimed that vaso-constrictor fibers are supplied by the anterior bundles of the ganglion. Obviously, section of the sympathetic nerve would cause vaso-dilatation. On the same basis, an increase of saliva would occur because of the increased blood supply to the salivary glands after section of the sympathetic nerve fibers.

FIG. 3. IRON HEMATOXYLIN AND VAN GIESON STAIN. LONGITUDINAL SECTION OF THE PERIPHERAL SEGMENT TO SHOW THE PROLIFERATION OF THE NEURILEMMA

After section of the post-ganglionic nerve fibers, the usual paralytic symptoms appeared immediately. The pupil on the affected side became much smaller, the ear was much warmer, the eyelids were closer together, and the nictitating membrane projected about one-fourth to one-half of the distance over the cornea. Increased lacrimation, sneezing and drooling were observed on the following day.

Changes in the appearance of the pupil (*fig. 5*). The rate and extent of recovery from the primary sympathetic nerve paralysis varied in

the eighteen cases in which the cut ends of the post-ganglionic fibers were united. However, this variation was relatively slight. The earliest return to equality occurred after forty-nine days in two cats; the longest time necessary was seventy-six days; the average was fifty-six days. The small pupil which was immediately present after operation persisted for one or two weeks. From the second or third week recovery gradually took place, but this progress was extremely

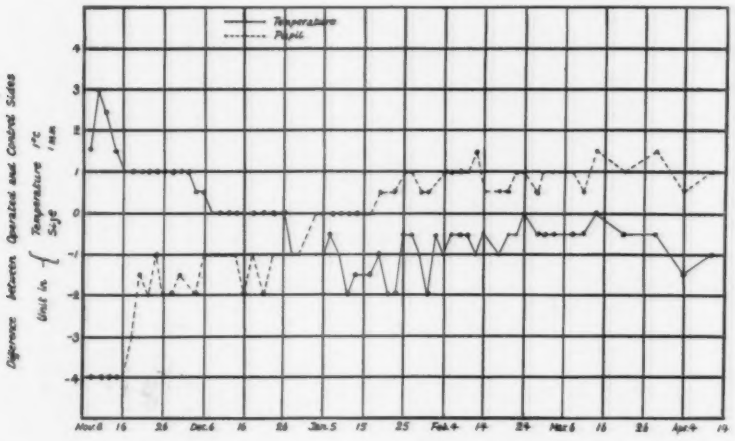

FIG. 4. CHART TO SHOW THE DIFFERENCES IN TEMPERATURE, AS WELL AS THE SIZE OF PUPIL, BETWEEN THE SIDE OF OPERATION AND THE CONTROL

Note that the temperatures of the ears became equal before the pupils were of the same size. This chart also shows that after regeneration had taken place the temperature of the ear on the side of the lesion became less than that of the control and continued so. It also illustrates how the pupil on the side of the operation remained larger than the normal one.

slow. After the pupils became equal they remained thus for a day or even as long as a week, but after this time the pupil on the side of the lesion became larger, and although it gradually became smaller again, it never reached a permanent equality even though the pupils were occasionally equal. In one animal permanent equality had not occurred after 253 days. In another the pupils were equal on the thirtieth day, but examination showed that one small branch of the

post-ganglionic fibers had not been sectioned. This remarkable compensatory development will be dwelt on later. Occasionally, the pupils became transitorily equal for a day or even a week at unexpected times; however, stimulation of the pre-ganglionic fibers at such times failed to show regeneration. That an explanation for such a paradoxical phenomenon can be found in the work of Anderson or of Byrne is doubtful. Furthermore, when a one per cent solution of cocain was put into the conjunctival sac of the affected eye, a slight pupillary reaction occurred, due to stimulation of the myo-neural junction (Brodie and Dixon). When cocain was applied after regeneration had taken place and the pupils were equal, then the pupil on the operated side reacted more than the control side. Possibly this disproportion was due to "over-function."

Changes in the nictitating membrane. In every case the nictitating membrane projected from one quarter to one-half over the cornea. This protrusion gradually became less marked, a distinct improvement being frequently observed at the end of one week. In all cases such an improvement always appeared by the third week. The normal position was then assumed as early as the third and as late as the sixth week. However, the position of this membrane varied considerably with the mental state of the animal; for when the animal was drowsy the membrane was unusually prominent, whereas it was more retracted when the cat was excited.

Changes in the temperature of the ear. A higher temperature was always observed immediately after operation in the ear on the side on which the operation had been performed. Usually from the tenth to the fifteenth day a decrease in this temperature was noted, this difference gradually becoming less until as early as twenty days and as late as forty days the temperatures of the ears were equal. On an average this equality was reached in twenty-four days, but it was not constant, for although it may have remained stationary for a week or even two, at the end of that time a lower temperature was always found on the side of the lesion as long as the animal remained alive. In contrast to the work of Lee on the section of pre-ganglionic fibers where differences of temperature between the two ears reached 8 degrees centigrade, the greatest difference in temperature after section of the post-ganglionic fibers was 3.5 degrees. At times the tempera-

FIG. 5, *a*. TO SHOW THE CHANGES IN THE APPEARANCE OF THE EYE AFTER SECTION AND REGENERATION OF THE POST-GANGLIONIC CERVICAL SYMPATHETIC NERVE FIBERS

Note that in the last picture taken ten weeks after operation, the pupil on the side of the operation was larger than the one on the control side.

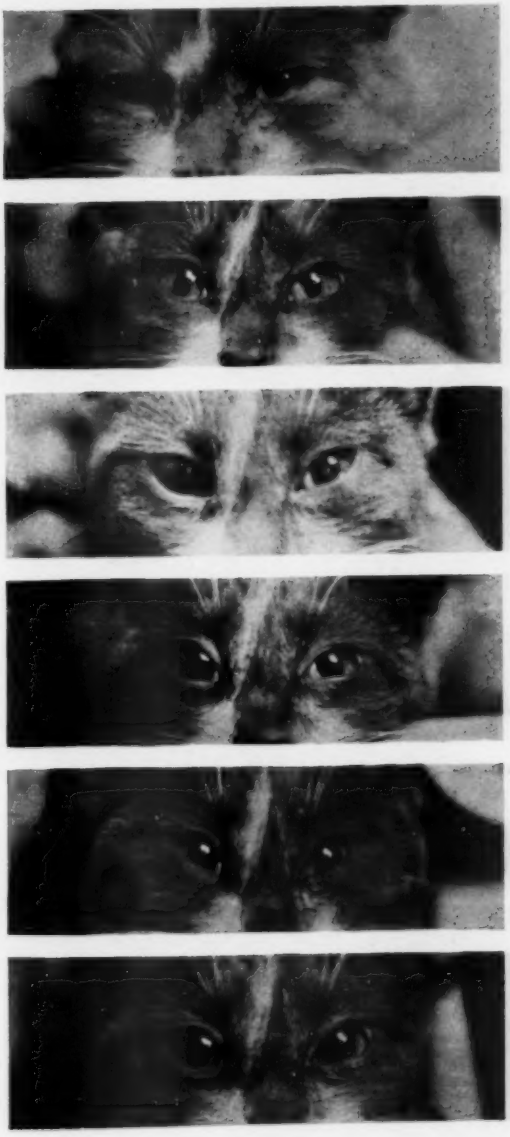

FIG. 5, *b*.

TABLE I

Experiment 7

DATE	TEMPERATURE OF EARS		DIAMETER OF PUPILS		DEGREE OF PROJECTED N.M.	OTHER PARALYTIC SYMPTOMS	REMARKS
	Right	Left	Right	Left			
days	°C.	°C.	*mm.*	*mm.*			
1st	33.0	37.0	10.0	6.0	1/3	L.S. (+), Sal. (+), Sn. (+), L. eyelids closer	All paralytic symptoms are marked
1 w.	34.0	35.5	10.0	6.0	1/4	L.S. (−), Sal. (−), Sn. (−), L. eyelids still closer	Paralytic symptoms (except pupil) slightly diminished
2 w.	32.0	32.5	7.0	4.0	A little	As before	
3 w.	32.5	33.5	7.0	5.0	A little	L. eyelids still closer	L. eyeball seems to be retracted
4 w.	30.5	31.5	7.0	5.0	Normal	L. eyelids still closer	N. M. normal
5 w.	35.0	35.0	4.0	3.0		L. eyelids little closer than right	Both ear temps. are equal
6 w.	35.0	35.0	5.0	4.0			Both ear temps. are equal
7 w.	33.0	33.5	6.0	5.0			L. ear temp. little higher than right
8 w.	31.0	30.0	6.0	5.0		L. eyelids little closer	L. ear temp. lower
9 w.	33.0	33.0	6.0	5.0		Both eyes open equally	
69th	31.0	31.0	7.0	7.0		Both eyes open equally	Both pupils are equal
10 w.	33.5	31.0	4.0	4.5		L. eyeball protrudes	L. pupil larger; L. eyeball protrudes
71st	38.0	36.0	5.0	6.0		L. eyeball protrudes	Cocain test to both pupils; R. 6.0; L. 10.0 mm.
73rd	33.0	32.0	5.0	6.0		L. eyeball protrudes	Stimulation of l. c.p. caused reaction on pupil and N.M.
11 w.	32.0	31.0	6.0	8.0		L. eyeball protrudes	
12 w.	37.0	35.0	6.0	8.0		L. eyeball protrudes	L. eyelids open wider; L. eyeball protrudes
13 w.	35.5	35.0	6.0	7.0		L. eyeball protrudes	
14 w.	35.5	35.0	6.0	6.5	Normal		Both pupils almost equal
15 w.	31.0	30.0	6.0	6.5			
16 w.	30.0	30.0	5.0	5.5			Left eyeball protrudes
20 w.	35.0	32.5	6.0	6.5			From 16 w. to 20 w. same conditions continued

TABLE I—*Continued*

DATE	TEMPERATURE OF EARS		DIAMETER OF PUPILS		DEGREE OF PROJECTED N.M.	OTHER PARALYTIC SYMPTOMS	REMARKS
	Right	Left	Right	Left			
days	°C.	°C.	mm.	mm.			
(175th)	35.0	35.0	3.0	3.5			Both pupils equal; temp. of ears equal; cocain test: R. 4.0 mm., L. 5.5 mm. L. pupil still reacted stronger with cocain
(210th)	35.5	35.0	5.0	5.5			Cocain test: R. 6.0, L. 6.5
253rd	35.0	34.0	3.0	3.5		Still alive, exophthalmos of L. eye still continues	Cocain test: R. 4.0, L. 4.5

tures would be unexpectedly equal for a day or two at a time. It is difficult to state, therefore, exactly when the temperatures became equal, but certainly equality always occurred before the thirty-fifth day, and always before the pupils were equal.

The other paralytic effects such as sneezing and drooling lasted only for the first week as a rule; in a few cases salivation was noticed for two weeks. The enophthalmos, exophthalmos and ptosis varied directly with the pupillary change.

From these data it is plain that the recovery in tone of the various muscles supplied by the post-ganglionic sympathetic nerve fibers can be explained on the basis of nerve regeneration. It is interesting to note that suture of the sectioned nerve-ends, in contrast to letting them remain retracted for a few millimeters, did not hasten regeneration.

For the sake of example, the abbreviated protocol of one animal is given:

Experiment 7. Immediately after section of the left post-ganglionic cervical sympathetic nerve fibers, the left ear became flushed and warmer than the one on the control side; the left pupil became smaller, the eyelids were closer together

and the nictitating membrane projected a third of the distance across the cornea. On the following day the left pupil was still smaller and the left eyelids were still closer together. The nictitating membrane had not changed its position. There was a marked salivary and lacrimal secretion, as well as much sneezing. On the fourth day, the nictitating membrane was only one-fourth over the cornea, whereas, the other signs of paralysis were as before. In the accompanying table the abbreviations are as follows:

L.S., lacrimal secretion
Sal., salivation
Sn., sneezing
L.C.P., left cervical preganglionic sympathetic nerve fiber
N.M., nictitating membrane
Rt.Pl., right pupil
Lt.pl., left pupil
W., week

Table II is intended to give a brief summary of eighteen animals; and primarily to show the time required for the return of function.

Additional experiments were made to study the nature of the nerve fibers which were in the external carotid branch of the superior cervical ganglion. The usual paralytic symptoms of the eye took place immediately after section of the anterior branches of the left superior cervical ganglion, but since the external carotid branches had been spared, the temperature of the ears remained the same. Stimulation of these nerve fibers at once caused a constriction of the vessels in the ear and it became pale and cold, but the size of the pupil did not change. On the other hand, stimulation of the cut end of the anterior branches did not affect the temperature of the ear, but it did cause the pupil to become larger. These observations were noted in four animals and it is accordingly believed that the vaso-constrictor fibers to the blood-vessels of the ear are supplied only by the external carotid branches of the superior cervical ganglion, and that these same branches do not innervate any structures of the eye.

Experiments were also made to determine the distribution of nerve fibers in the anterior branch of the post-ganglionic fibers. As mentioned above, this branch has three divisions. When one or two of these divisions were cut, the pupil at once became smaller. In one animal, the lateral and middle branches were cut and twenty-one days later the pupils were equal. In another animal the dorsal and lateral branches were divided, but in this case the paralysis of the

pupil was not so great, since it was equal to the control side after three days. In a third cat the middle branch alone was divided, and fifteen days later the pupils were equal again. All the above described paralytic symptoms were less than when all the fibers were cut, indicating that all three branches carried fibers to the iris, and that section of one or two branches produced a compensatory activity in the remaining division.

TABLE II

NUMBER	TIME NEEDED FOR EQUALITY OF TEMPERATURE OF EARS	TIME NEEDED FOR LOWER TEMPERATURE OF LEFT EAR	TIME NEEDED FOR EQUALITY OF PUPILS	TIME NEEDED FOR LARGER STATE OF LEFT PUPIL	NUMBER OF DAYS TO AUTOPSY	REMARKS (SUTURE (+) OR NOT (−))
	days	*days*	*days*	*days*	*days*	
2	32	49	69	74	77	(−)
3	35	56	50	63	70	(−)
5	28	50	49	58	57	(−)
6	28	30	30	56	58	(−)
7	35	56	69	71	253 (still alive)	(−)
8	34	57	56	63	175	(−)
9	35	53	75	77	130	(−)
10	45	56	76	89	112	(−)
13	45	59	56	59	70	(−)
14	33	55	49	56	140	(−)
15	42	49	58	63	90	(−)
16	40	48	50	58	105	(−)
17	35	42	70	84	155 (still alive)	(−)
19	32	40	61	70	73	(−)
22	42	59	59	65	70	(−)
27	33	56	58	63	84	(+)
28	39	50	55	56	70	(+)
34	30	48	62	75	101 (still alive)	(+)

Degeneration and regeneration of post-ganglionic fibers (figs. 1–4). Immediate stimulation of the distal nerve segment after section showed the usual reaction of the pupil. Twenty-four hours later a weak current produced only a slight dilatation; in another animal the same response was had with a strong current. After forty-eight hours no pupillary response to even a very strong current was obtained. Apparently, irritability of the nerve fibers disappeared twenty-four hours after division.

Histologically, fragmentation of the axis-cylinders in the distal segment as well as in the proximal segment at the point of division was observed after twenty-four hours. In both areas many axones were found irregularly enlarged and swollen. After forty-eight hours the fragmentation had increased, many axones being entirely fragmented. Particles of various sizes and shapes representing degenerated axones were numerous. On the seventh day no intact axis cylinder was found anywhere in the distal segments; many of the fragments had entirely disappeared. The neurilemma cells had not changed very much; fibroblasts and particularly wandering cells appeared. By the fourteenth day the fragments had almost entirely disappeared. In the proximal segment by this time a few small new nerve fibers, frequently arranged in bundles of five to twenty, appeared in the connective tissue between the sectioned nerve ends, growing out from the direction of the ganglion. These bundles were surrounded by a covering which occasionally showed a nucleus. These regenerated fibers resembled those seen by Lee in regeneration of the pre-ganglionic fibers. By the twentieth day the number of new fibers had increased markedly, some had a fine myelin sheath which was thin and interrupted. These newly regenerated fibers could be traced across the defect between the nerve ends.

LITERATURE AND DISCUSSION

In 1904 Langley stated that stimulation of the anterior strands of the superior cervical ganglion caused constriction of the blood vessels in the ear. Accordingly, he concluded that the vaso-constrictor fibers to the vessels of the ear were supplied by the anterior strands as well as by the external carotid branches of the superior cervical ganglion. However, we have been unable to confirm this observation in all details because in four animals the vaso-constrictor fibers were present only in the external carotid branches. That this difference may be accounted for by structural variation in the animals seems doubtful.

The literature on the temperature changes in the ear following section of the post-ganglionic cervical sympathetic nerves is very meager. In 1897 Langley simply stated that twenty-four hours after section of these nerves no difference in temperature between the two

ears could be observed. In our series we were able to detect a difference in temperature amounting to two or three degrees ten days after the operation. This difference gradually became less, and on the thirty-fifth day the temperatures were equal again. However, this equality was not maintained, for subsequently the ear on the side of the lesion became colder and this relative difference remained present even for the cat which was kept as long as 253 days. As far as could be determined from a search of the literature, such an observation has not been made previously. However, it is difficult to give a satisfactory explanation for this phenomenon. It is possible that Langley's suggestion may be helpful for he believed that post-ganglionic fibers ending in any tissue may, during the process of regeneration, form endings with other tissues; so that, for example, pilo-motor fibers may form nerve endings in the iris and dilate the pupil.

Experiments dealing with the recovery of the size of the pupil have been reported before, chiefly by Langley, and by Tuckett. Langley found that it required nineteen weeks for the pupils to become equal, and ten weeks before only a slight difference was present. Tuckett in 1895 found that in rabbits 231 and 259 days after section of the anterior strands of the superior cervical ganglion, the pupils became equal and stimulation of the cervical sympathetic chain caused dilatation of the pupil. In contrast to these investigators, we found that regeneration had taken place much earlier, never later than 76 days, and as early as 49 days. Some of this discrepancy may have been due to the type of animal used, particularly since Tuckett experimented on rabbits.

Particular attention must be called to the phenomenon of persistent enlargement of the pupil after regeneration, as evidenced by stimulation of the cervical sympathetic chain, had taken place. In one cat, this condition persisted for 253 days after operation. The enlargement of the pupil is also accompanied by a moderate exophthalmos and marked retraction of the nictitating membrane. This condition has been described before by Lee, but in his series of cases the regeneration was of the pre-ganglionic fibers, and the condition was temporary. An explanation of this phenomenon is still needed, even though the suggestion of Langley mentioned above must be given serious consideration.

As regards the increase in lacrimal and salivary secretions with the attendant sneezing which, according to Langley (1898), ceased after two or three weeks, in our series these effects never were present longer than one week. Whether this increase of secretions was due to a reflex excitation of a central secretory center (Langley, 1885) seems less likely than an explanation which draws upon the increased blood supply following section of the sympathetic fibers.

Langley had previously noted that the ptosis on the injured side disappeared with recovery of the pupil, but since he never observed the exophthalmos nor the increased size of the pupil, it is impossible to make any comparison.

Histological control of the phenomena of degeneration and regeneration has not been stressed in previous investigations. Tuckett (1895) stated that degenerative changes appeared twenty-four hours after section, that the axis cylinder disappeared but that the neurilemma was unaffected. He did not deal with regeneration. Langley and Anderson (1899) said that the non-medullated nerve fibers showed no striking evidence of degeneration, the fibers in the distal segment simply dwindled away, occasionally becoming finely granular. They also disregarded a study of the regenerative processes. In our experiments it was found that histological and physiological degeneration seemed to begin about twenty-four hours after section, while definite outgrowth of new fibers was not observed until the fourteenth day. The neurilemma was essentially unchanged (figs. 1 to 4). When compared with the speed of regeneration of cerebrospinal nerves (Howell and Huber, 1893) that of the sympathetic nerves is frequently faster.

CONCLUSIONS

From a study of eighty-four cats in which the post-ganglionic fibers of the cervical sympathetic chain were sectioned, it was found that the vaso-constrictor fibers to the blood vessels of the ear were supplied by the external carotid branches of the superior cervical ganglion.

Recovery from the paralytic symptoms required on an average about fifty-six days; the earliest return of function was noticed after forty-nine, and the latest after seventy-six days. Electrical stimulation of the pre-ganglionic fibers aided in determining the rate of regeneration.

A large pupil, exophthalmos, and constriction of the ear vessels persisted for a long time after the signs of paralysis had disappeared. It is believed that a way for the experimental production of exophthalmos may thus have been found. A satisfactory explanation for this phenomenon is still wanting.

Histological control of the processes of degeneration and regeneration showed that degeneration took place about twenty-four hours after section, and that regeneration was well established by the fourteenth day, myelinization having been observed by the twentieth day.

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BOOK REVIEWS

The Blood Vessels of the Human Skin and Their Responses. By THOMAS LEWIS, M.D., F.R.S., Physician of the Staff of the Medical Research Council; Physcian of University College Hospital. *London: Shaw & Sons Ltd.*, 7, 8 & 9, *Fetter Lane, Fleet Street, E. C.* 4, 1928.

Sir Thomas Lewis has said that the great flaws in clinical pathology today consist of "an unusual craving and veneration for hypotheses, inexact observation and prematurity of conclusion."

This volume devoted to the physiology of the vessels of the skin illustrates in a remarkable way the antithesis of the axioms in the quotation above. It represents the end results of studies covering a period of eleven years, carried out with the exhaustive thoroughness, detailed observation, and critical analysis so characteristic of all of Sir Thomas's contributions to Medical Science.

There is no single volume nor indeed any text in any way at all comparable to this work and though there may exist differences of opinion as to the finality of the answer given in these pages to the mechanism involved in certain of the skin reactions, the evidence for the conclusions arrived at is marshalled in logical sequence and described with great clearness. In the interpretation of evidence of the sort available for the conclusions drawn, great attention to the detailed description of the observations is necessarily essential, and there are occasional passages in which the descriptive minutiae demand very careful and close reading.

The main theme of the text taken in its entirety is an argument for the existence of the H or histamine-like substance as the important factor in most of the skin reactions encountered. The chapter devoted to the H substance activities is an extremely interesting survey of the evidence supporting the author's hypothesis. The statement that herpes zoster results from release of the same substance following irritative lesions of the sensory nerves involved is but one of many suggestive inferences.

The confusion in the past in the interpretation of the local reactions of blanching, flare and whealing is swept away and we have at last an apparently perfectly satisfactory explanation of the physiology involved.

This volume can not be too enthusiastically commended and should be carefully read by every one at all interested not only in the elucidation of a number of obscure but common manifestations of skin reaction, but as an exposition of the method of deductive reasoning applied to hitherto but little understood clinical phenomena.

E. P. C.

The Respiratory Function of the Blood. Part II. Haemoglobin. By JOSEPH BARCROFT. 200 pp. (*Cambridge: University Press*, 1928.)

Instead of putting under one cover a revision of his *The Respiratory Function of*

the Blood Professor Barcroft is publishing its subject matter in a series of which the book which he refers to as *Haemoglobin* is the second. The first, *Lessons from High Altitudes*, appeared in 1925.

Haemoglobin deals, for the most part, with the more generally familiar physical-chemistry of haemoglobin solutions; but the first three chapters review one of those unfoldings of science which make stuffy journals fascinate the investigator more than detective stories—to the amazement of laymen.

It is the story of investigations which have established not only the specificities of blood pigments but the essential similarities upon which an ordered view of structure and conduct is being built. It now seems probable that the porphyrins are well nigh universal constituents of cells and appear here in combination with iron, there with copper, or exceptionally with manganese or other metals, and with specific proteins. "Sherlock Holmes himself," says Barcroft, "could not make a more dramatic appearance than that of a blood pigment in a mixed company of yeast cells, bacteria and onions."

Told in Barcroft's best style the story makes exciting reading. The historical setting is especially valuable; but in justice to the subject two faults of the presentation must be mentioned. Dramatic interest has so far obscured prosaic systematic presentation as to leave the reader a bit confused. This might have been avoided had more space been devoted to the work of Hans Fischer and his students. While it was only last December that cable dispatches announced Fischer's synthesis of haemin, his basic researches had progressed to a point where good use could have been made of that great systematizer of chemical thought—structural organic chemistry.

A trace of the first criticism will be seen to apply in the subsequent chapters upon the physical chemistry of haemoglobin solutions. Experimental data of historical importance are introduced to reveal the evolution of ideas; but, for an age when busy students demand succinct summaries of the best available numerical data, the necessity of searching the text of several chapters to separate data of historical from those of concrete importance is a bit confusing.

The preoccupation with certain historical developments has left a number of subjects without adequate treatment. Among these may be mentioned Conant's electrochemical treatment of the hemoglobin-methemoglobin system and Redfield's researches on hemocyanin. More detail regarding apparatus and technique would have been welcomed.

However, the above criticism is engendered by the wish that more aspects of the subject could have received the enlivening touch of Professor Barcroft's pen. That he did not choose to deal at greater length with certain topics or to freeze into definitive schematic form the data of subjects which are still molten is not only his right as an author but perhaps the choice of mature wisdom. What he has accomplished above all else is to make his reader feel that the subject is alive with interest and that the present is the period of its making.

W. M. C.

The Examination of the Central Nervous System. By DONALD CORE, M.D., Manc., F.R.C.P. Lond. 248 pp. $3.50. (*William Wood and Company, New York, 1928.*)

The *Examination of the Central Nervous System* by Donald Core, lecturer in Neurology, University of Manchester, is intended for the use of students at the beginning of their study of clinical neurology. It is clearly and concisely written, practical in technique and helpful in analysis of some common disorders.

Especially is this true in the discussion of types of tremors and incoördinations, including cerebellar and labyrinthine forms, of the characteristics of posture and the causes of impaired muscle control.

Under the general head of Reflexes the author outlines the central connections of deep and superficial reflexes, giving also a good short account of conditions altering the reflexes, and the analysis and correlation of various possible combinations of results of examinations.

The technique of examination of the sensory system is exceedingly detailed and valuable. Dr. Core gives a thoughtful review of the subjective complaints of patients with their probable causes, and analyzes types of sensory loss in lesions of the cord and the localization of such lesions.

One chapter is devoted to observations on ophthalmoscopic findings in diseases of the central nervous system, the study of visual fields and hemianopsia and causes of inequality of the pupils.

There are also short chapters on Speech, the Mental State of the patient, Cerebro-Spinal fluid and Electrical Reactions.

In one particular the book fails to be helpful to a student of neurology, for in the examination of the patient as a whole there is no attempt to consider neurological entities. The author has a disconcerting method of beginning the examination of some cranial nerves, passing to the muscles of the upper extremities, to the heart, lungs, lower extremities and finally ending with cranial nerves again—the eighth pair and taste elements of the seventh! Such haphazard methods of examination may be entirely safe in the hands of a neurologist but they are misleading to students at the beginning of training.

C. Mc.C.

The Kahn Test. A Practical Guide. By R. L. KAHN, M.S., Sc.D. 201 pp. $4.00. (*The Williams & Wilkins Company, Baltimore, 1928.*)

In this work, the author combines a detailed laboratory guide for the performance of the Kahn precipitation test, with an ingenious theoretical discussion of the supposed principle underlying the precipitation phenomenon in general, and more particularly in syphilis. An attempt is made to explain precipitation in syphilis as a pure adsorption process, in which antigen acts as a colloidal solution of lipoids, the invisible particles in which are aggregated by syphilitic reagin, a hypothetical substance, contained in blood serum, cerebrospinal fluid, or other body fluids. The findings of numerous workers are reviewed, tending to support the view that in syphilitic infection both protein and lipoid antigens exist, which conform to the laws of other known protein antigen-antibody reactions. Methods of prepara-

tion and standardization of antigen are given in detail, and some new simplified modifications are outlined. Complete instructions for the routine performance and interpretation of the test are given, as well as micro methods, quantitative modification, provocative procedures, and the adaptation of the test to the cerebrospinal fluid.

The popularity of the Kahn test has become so widespread, and its worth so firmly established, especially since the favorable report of the Laboratory Conference on the Serodiagnosis of Syphilis, arranged by the League of Nations Health Committee, that a book of this kind will be welcomed by both physician and laboratory workers.

H. H. H.

René Théophile Hyacinthe Laennec. A Memoir. By GERALD B. WEBB, M.D. 146 pp. $2.00. (*Paul B. Hoeber, Inc., New York, 1928.*)

To a number of volumes that have previously appeared, Cadogan's Essay on Gout by John Ruhräh, Thomas Sydenham by David Riesman, Adolf Kussmaul by Theodore H. Bast and Max von Pettenkofer by Edgar Erskine Hume, the publishers now add a brief account of the life and work of René Théophile Hyacinthe Laennec. In the small space of one hundred and forty-six pages is compressed the story of this great man, the story of a life so human and so simple that it is almost commonplace, the story of a work so original and so comprehensive that it revolutionized medical practice. Thomas Addison proclaimed that Laennec contributed more toward the advancement of the medical art than any other single individual either of ancient or of modern times. Laennec is just the sort of physician that we ourselves would like to be, studious and unostentatious, quietly observing and analyzing, tirelessly applying and demonstrating his new method of examination. But I wonder, had we lived in 1820 in Paris, if we would have had the good sense to prefer making rounds with him at the Necker to sitting in the amphitheatre and listening to the passionate eloquence of Broussais and his violent abuse of Laennec. The chances are we should not have had such good sense, for very few displayed it. Laennec's discovery met with indifference from the learned and with ridicule from the stupid. Physicians who used the stethoscope, patiently confirming Laennec's observations, were regarded as charlatans. His following was made up of more foreign than native students. What we know of the personal and intimate life of Laennec we owe to the indefatigable and painstaking investigations of Rouxeau. His studies, based on the family letters and papers, have been published in two volumes and give an authentic portrait. Here we find not the cold, intellectual man of tradition, but an ardent, enthusiastic student and physician, working hard and eagerly at his medical problems, not despising but neglecting the opportunities for financial reward from practice.

It is a delight to read of Laennec and his work in this charming volume of Webb. The story is told engagingly and with sympathy and enthusiasm. Every physician and most laymen will find it deeply interesting, almost exciting, and far more pleasing and satisfying than most short stories.

L. H.